

**Application of Lean and Continuous Improvement Methodologies at a  
Biopharmaceutical Manufacturing Site**

By

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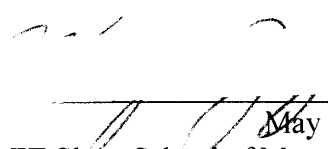
Submitted to the MIT Sloan School of Management and Department of Chemical Engineering  
in partial fulfillment of the requirements for the degrees of

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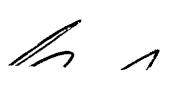
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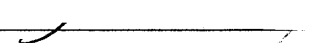
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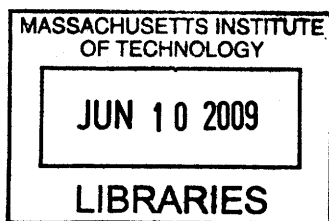
  
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## **Abstract**

Heightened competitive pressures, changes in the regulatory atmosphere, and dropping research and development productivity have been plaguing the pharmaceutical and biotechnology industries. Amgen has felt the effects of these forces and launched a new effort to improve its operations via continuous improvement and Lean, ultimately reducing costs and improving productivity of operations. This thesis examines one example of a process improvement effort at Amgen's Fremont manufacturing facility. This project involved characterizing the cycle times of their buffer solution preparation processes, leading to targeted actions to both minimize variability in the process and to reduce the amount of time and effort to manufacture tanks of buffer solution. Tools and ideas from Lean and Six Sigma were applied and a prioritized action plan was presented to the company. This thesis also provides a broader examination of how such continuous improvement efforts can fit into the biotechnology industry with its idiosyncrasies.

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## **Note on Proprietary Information**

In order to protect proprietary Amgen information, the data presented throughout this thesis have been altered and do not represent the actual values used by Amgen. The product, process steps, operational efficiencies, cycle times, and dollar values have been disguised in order to protect competitive information where necessary.

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## Table of Contents

<b>ABSTRACT.....</b>	<b>3</b>
<b>ACKNOWLEDGEMENTS.....</b>	<b>5</b>
<b>NOTE ON PROPRIETARY INFORMATION .....</b>	<b>7</b>
<b>TABLE OF CONTENTS .....</b>	<b>9</b>
<b>TABLE OF FIGURES .....</b>	<b>10</b>
<b>CHAPTER 1: INTRODUCTION .....</b>	<b>11</b>
1.1 LFM PROGRAM & AMGEN .....	11
1.2 PROBLEM STATEMENT .....	11
1.3 APPROACH.....	12
1.4 THESIS OVERVIEW .....	14
1.5 LITERATURE REVIEW .....	14
<b>CHAPTER 2: BACKGROUND.....</b>	<b>16</b>
2.1 BIOTECHNOLOGY INDUSTRY BACKGROUND .....	16
2.2 MANUFACTURING BACKGROUND .....	21
2.3 ORGANIZATION OF OPERATIONAL EXCELLENCE AT AMGEN.....	24
<b>CHAPTER 3: BUFFER PREPARATION PROCESS IMPROVEMENT.....</b>	<b>27</b>
3.1 INITIATE .....	27
3.2 BASELINE CURRENT STATE .....	28
3.3 DESIGN FUTURE STATE .....	44
3.4 SCOPE, PRIORITIZE, AND AGREE .....	50
3.5 IMPLEMENT AND CLOSEOUT .....	52
<b>CHAPTER 4: CONCLUSIONS AND RECOMMENDATIONS.....</b>	<b>54</b>
4.1 AMGEN FREMONT .....	54
4.2 AMGEN OPERATIONAL EXCELLENCE .....	55
4.3 CONCLUSION .....	57
4.4 RECOMMENDATIONS FOR FUTURE WORK.....	58
<b>APPENDIX: LABOR MODELING AND BALANCING AT AMGEN OPERATIONS.....</b>	<b>59</b>
A.1 CONCEPTS OF MODELING LABOR FOR BATCH PROCESSES.....	59
A.2 OPPORTUNITIES FOR STANDARDIZATION .....	60
A.3 CONCLUSION .....	60
<b>BIBLIOGRAPHY .....</b>	<b>63</b>

## Table of Figures

FIGURE 1: RECOMBINANT DNA TECHNOLOGY .....	17
FIGURE 2: ANALOGY OF MOLECULAR SIZE AND COMPLEXITY TO TRANSPORTATION MODES .....	19
FIGURE 3: PHARMACEUTICAL NEW DRUG APPROVAL PROCESS (FDA).....	20
FIGURE 4: ANTIBODY-A GENERALIZED PROCESS FLOW.....	23
FIGURE 5: AMGEN'S OPERATIONAL EXCELLENCE FRAMEWORK.....	25
FIGURE 6: VSM OF AFR PURIFICATION .....	27
FIGURE 7: BUFFER PREPARATION PROCESS MAP .....	29
FIGURE 8: BUFFER PREP PROCESS CHRONOLOGY TO QUANTIFY CYCLE TIMES .....	35
FIGURE 9: SAMPLE CYCLE TIME BOX PLOT, BY BUFFER TYPE .....	38
FIGURE 10: BUFFER PREP CYCLE TIME BREAKDOWN BY STEPS .....	39
FIGURE 11: SAMPLE FLOW RATES FROM PREP TANK TO HOLD TANK.....	41
FIGURE 12: FILTER MANUFACTURER'S RATED FLOW FOR FILTER CARTRIDGES.....	42
FIGURE 13: EXAMPLE OF PRESSURE INDICATOR READING OVER TIME DURING A TRANSFER .....	42
FIGURE 14: DIAGRAM OF BUFFER TRANSFER OPERATION, ELEVATION EFFECTS .....	43
FIGURE 15: BUFFER PREP STANDARD WORK VISUALIZATION .....	46
FIGURE 16: EXAMPLE OF POSSIBLE AIR ACCUMULATION EFFECTS ON FILTER PERFORMANCE (TANK LEVEL).....	48
FIGURE 17: PRIORITIZED BUFFER PREP IMPROVEMENT LIST TO AFR.....	52
FIGURE 18: EXAMPLE VISUALIZATION OF LABOR LOADING MODEL .....	59
TABLE 1: PRELIMINARY OPPORTUNITY LIST.....	31
TABLE 2: BUFFER PREP SAMPLE SET.....	33
TABLE 3: BUFFER PREP PRODUCTION CYCLE TIME FACTORS .....	34
TABLE 4: PROCESS STEPS AND IMPROVEMENT OPPORTUNITIES .....	35
TABLE 5: FILTER FLOW RATE BY BUFFER TYPE .....	43
TABLE 6: FILTER FLOW IMPROVEMENT ANALYSIS.....	47



# **Chapter 1: Introduction**

## ***1.1 LFM Program & Amgen***

The Leaders for Manufacturing (LFM) program is a partnership between the Massachusetts Institute of Technology (MIT) School of Engineering, MIT Sloan School of Management, and 23 supporting partner companies. LFM provides its Fellows with two degrees: an SM in Management or MBA, and an SM in one of several participating engineering disciplines.

Amgen Inc. is one of the LFM industry partners, and is a leading biotechnology/pharmaceutical company headquartered in Thousand Oaks, CA. Amgen manufactures innovative treatments for serious illnesses.

This thesis is the result of a six-month internship at Amgen Inc.'s Thousand Oaks, CA headquarters and Amgen's Fremont, CA manufacturing facility (AFR). The internship project is a continuation of the work by Adam Villa (Villa, 2008), who was previously an LFM intern at Amgen. Work was conducted in Amgen's Operations Improvement Group, which is tasked with the lean transformation of the manufacturing network in order to improve operating efficiency and ensure supply of high quality products for patients.

## ***1.2 Problem Statement***

The purpose of the internship was to participate in the Operations Improvement Department's continuous improvement activities. This included program development such as developing training curricula, and aligning Amgen's manufacturing network of seven clinical and commercial site activities (Amgen, Inc., 2008) to the Amgen Process Excellence (APEX) continuous improvement methodology. Aligning continuous improvement work to APEX has been an ongoing task along with increasing the Industrial Engineering and Lean capabilities across the manufacturing network through training and targeted projects that started during Adam Villa's tenure as an LFM intern (Villa, 2008). The focus of this thesis is to build on (validate successes, etc.) these efforts by using work done at Amgen's commercial manufacturing site in Fremont, California as a detailed case study. Specific focus was given to

the buffer preparation process and to demonstrating the effectiveness of the APEX methodology along with related tools.

The AFR work focused on improving the process to produce a critical component, buffer solutions, used in purification of AFR's product "Antibody-A." The buffer preparation ("buffer prep") process improvement goal of cycle time reduction was prompted because buffer prep was identified as a bottleneck process from previous visits that included SME interviews, process reviews, and generation of value stream maps (VSMs). Once this focus area was identified, any other possible improvements to cost, quality, and speed were sought during the internship project. The buffer prep process is outside of the main flow of product through a biotechnology manufacturing plant. This is significant because modifications to processes in the main product flow usually have higher barriers to implement due to concerns about effects on product quality. Buffer prep processes are present in virtually all manufacturing plants for bulk biologically derived products and require significant resources in terms of capital equipment and operation. Therefore, work on the Fremont buffer prep process could be used as a best practice for the buffer prep processes in the entire Amgen manufacturing network.

Finally, the question of whether Lean is likely to succeed in the biopharmaceutical plant and reflection on Villa's hypothesis (Villa, 2008) with respect to Amgen's organizational profile in particular will be addressed in this thesis. The APEX methodology will be examined as a framework for continuous improvement, as well as the organization of the company-wide and plant-specific efforts. Recommendations to improve the chances for success at Amgen will also be proposed.

### **1.3 Approach**

The approach taken during the internship involved a combination of an Amgen-specific project management system and the application of analytical tools from statistical process analysis and Lean Manufacturing. Amgen Process Excellence (APEX) is a six-step project management methodology to promote a science-based approach to process improvement across the Amgen manufacturing network. This methodology was used to frame the progress of the project at AFR. APEX consists of six major phases and is similar to the DMAIC framework (Define,

Measure, Analyze, Improve, and Control) (Barney & McCarty, 2003) and Deming cycle (Plan, Do, Check, Act) (Womack & Jones, 2003):

1. Initiate
2. Baseline current state
3. Design future state
4. Scope, prioritize, and agree
5. Implement
6. Closeout

Supporting the APEX methodology is a toolkit selected from Lean and Six Sigma. Tools from Six Sigma include statistical data analysis such as visualization of data, project management tools such as structured data collection, listening to the voice of the customer, and structured brainstorming. Lean tools and topics include: value stream mapping, process mapping/SIPOC, 5S, standard work, cycle time analysis, and promoting employee involvement.

Remote project management via periodic interaction with the plant's managers and associates owning the buffer prep process was used for this internship project. During the data collection phase in order to "Baseline current state" and to "Design future state," key contacts—shift managers, the APEX lead at Fremont, and manufacturing associates—were essential for providing valuable information and immediate feedback to ensure the quality of analysis. These specific activities were done on site during two week-long visits. The plant data repository was remotely accessed from Thousand Oaks through secure networks in order to collect additional quantitative data from production records. Computer analysis of that data was accomplished remotely and periodically shared as progress was made. Similar methods to collect and analyze data can be leveraged by the OI group for future projects if an on-site project manager is not feasible, but having the project manager on site is the most desirable option.

Implementation of the process improvement suggestions was the responsibility of AFR personnel. An implementation plan is presented here, along with general information regarding change management and the risk-based approach promoted by the FDA. This discussion is

intended provide some understanding of how changes for process improvement can be handled in a highly regulated biotechnology manufacturing environment.

## **1.4 Thesis Overview**

This thesis is organized into the following chapters:

Chapter 1 provides an introduction to the thesis.

Chapter 2 provides background on the project: industry, company, and site context.

Chapter 3 provides deeper discussion on the buffer prep project approach and results.

Chapter 4 offers observations and recommendations based on the experience at both the site and company levels.

An Appendix contains an overview of another potential operational excellence project.

## **1.5 Literature Review**

The theme of this thesis is the implementation of continuous improvement methodologies, specifically Lean Manufacturing, in biotechnology operations. The distinction of implementation in the biotechnology industry is important because the biotechnology industry is highly differentiated from other traditional manufacturing industries where Lean and other continuous improvement methodologies have been widely applied. This differentiation is based on the nature of the products, process technology, and the degree of regulation due to the pharmaceutical application of biotechnology products.

There have been several books, articles, lectures, curricula, and businesses developed using the ideas of Lean, Six Sigma, and business process improvement. The Machine that Changed the World (Womack, Jones, & Roos, The Machine that Changed the World, 1990) introduced the term “lean” production as opposed to “mass production,” and focused on Japanese manufacturing methods that were far more efficient than American manufacturing methods in the automobile industry. Notable reference books in the Lean literature include Lean Thinking by Womack and Jones (Womack & Jones, Lean Thinking, 2003) and Learning to See by Rother and Shook (Rother & Shook, 1999). Each of these books offer discussion of both strategic, tactical, and change management aspects of lean transformations via case studies and some step-

by-step approaches. Lean and the Toyota Production System (TPS) are active fields of academic business research, and a framework was proposed by Spears and Bowen in the hopes of making Lean implementations more successful (Spears & Bowen, 1999). Six Sigma is also a widely applied methodology to improve the quality of products being manufactured and has been applied to improve other processes within business operations (Motorola, Inc.). A project management methodology and powerful statistical tools are frequently emphasized in applications of Six Sigma. Yet another improvement methodology from the business literature is the Theory of Constraints, discussed in The Goal by Goldratt and Cox (Goldratt & Cox, 1986).

Applications of Lean in biotechnology have been primarily documented in trade journals. Six Sigma was touted as a proven operational excellence strategy in pharmaceutical firms by DePalma (DePalma PhD., 2006). Shanley synthesizes pharmaceutical industry survey data regarding operational excellence efforts at multiple organizations and highlights the challenges of implementation (Shanley, 2008). Discussion of current good manufacturing practice (cGMP) regulatory environments and Lean Manufacturing was conducted by Greene and O'Rourke (Greene & O'Rourke, 2006). A growing body of knowledge in this specific area of Lean/Operational Excellence in biotechnology can also be found in theses written in conjunction with LFM. An excellent background on both the subjects of the pharmaceutical industry and operational excellence can be found in Coffey's thesis "Achieving Business and Operational Excellence in the Pharmaceutical Industry" (Coffey, 2008).

Finally, implementation of Lean in any environment brings the issue of change management and leadership. Klein uses research conducted at MIT to propose a better way to enact lasting change in an organization (Klein, 2004). Another work by Klein discusses the issues of globally dispersed teams, which many firms face when pursuing Lean (Klein & Barrett, One foot in a global team, one foot at the local site: Making sense out of living in two worlds simultaneously, 2001). Ongoing research and additional literature in the field of change management and leadership abound.

## Chapter 2: Background

This chapter provides background to help understand Amgen and the biotechnology industry. This will also provide additional context behind the project and drivers behind Amgen's shift toward operational excellence, including its continuous improvement efforts.

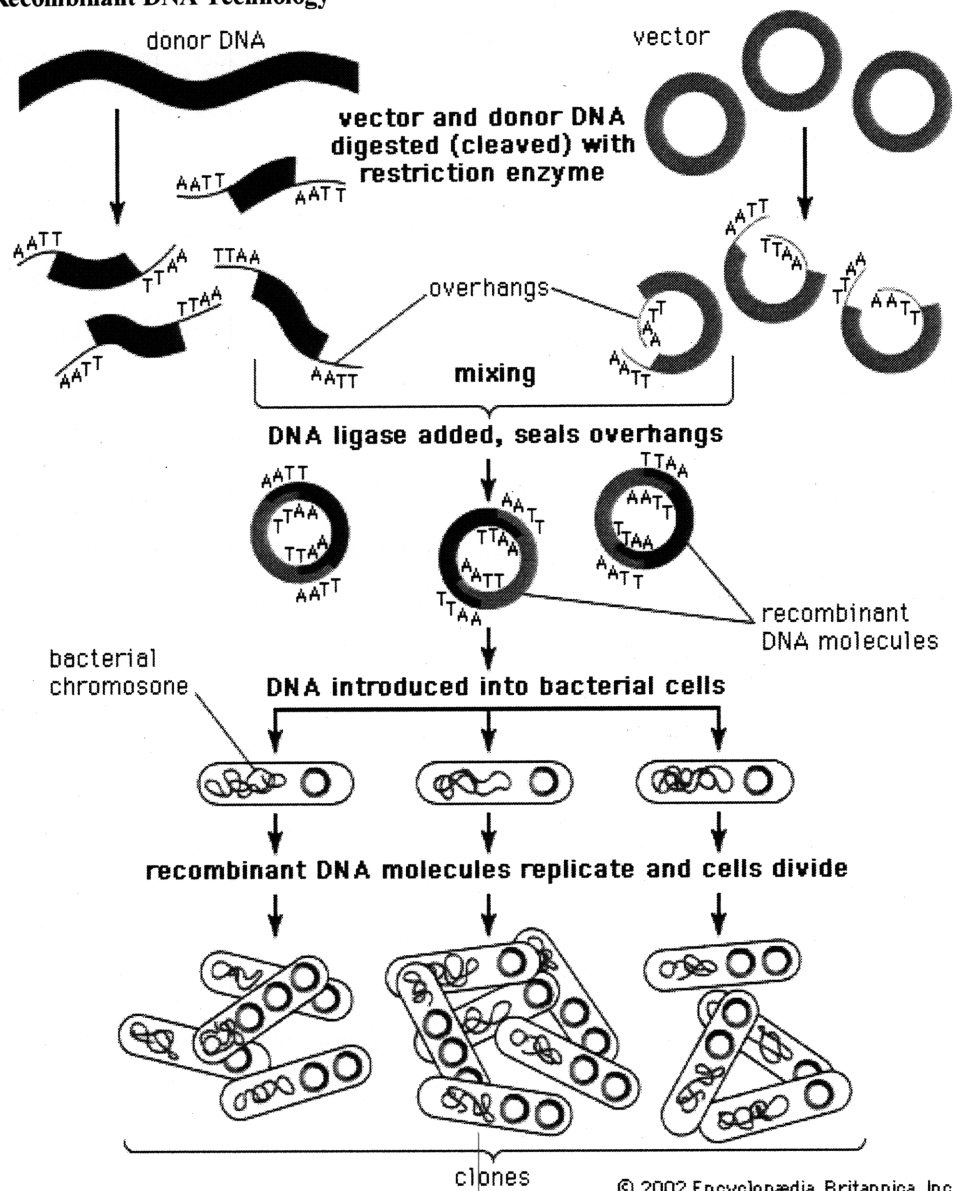
### ***2.1 Biotechnology Industry Background***

The biotechnology industry has its roots in fermentation products such as wine, beer, and lactic acid using organisms such as yeast and bacteria (*Saccharomyces cerevisiae* and *Escherichia coli*). The field of biochemical engineering is defined by the use of living organisms and their components such as enzymes to produce chemical or biological materials, as well as new process development. Today's biopharmaceutical industry was established based on scientific breakthroughs in recombinant DNA technology in the 1970s, allowing for genetic engineering of pharmaceutically active molecules. (Blanch & Clark, 1997)

#### *Basic Overview of Genetic Engineering and Biotechnology:*

The logic of biotechnology is based on discoveries in protein science and genetics. The genetic code to produce a protein of interest is programmed into a cell's DNA. The cell is replicated so that a large number of these genetically modified cells/organisms can produce the protein of interest in commercially viable quantities. A general schematic of recombinant DNA technology is shown below (Britannica, 2002) in Figure 1. Hormones such as human insulin and erythropoietin were synthetically produced by biotechnology companies such as Genentech/Eli Lilly (Thayer) in 1978 and Amgen in 1989 (Amgen, Inc.), respectively.

**Figure 1: Recombinant DNA Technology**



Further advances in molecular biology led to hybridoma technology, which is designed to produce synthetic monoclonal antibodies (MAbs), used for both commercial diagnostics and therapeutics (Blanch & Clark, 1997). A hybridoma is a hybrid cell, where an antibody-producing spleen cell is taken from a mouse and fused to an immortal cancerous myeloma cell (National Cancer Institute, 2006). The first MAb product Orthoclone OKT3 (muromab) made by Johnson & Johnson was approved in 1986 (Scott, 2007). Additional technological advances led to humanized MAbs to counteract the fact that early MAbs contained mouse genetic

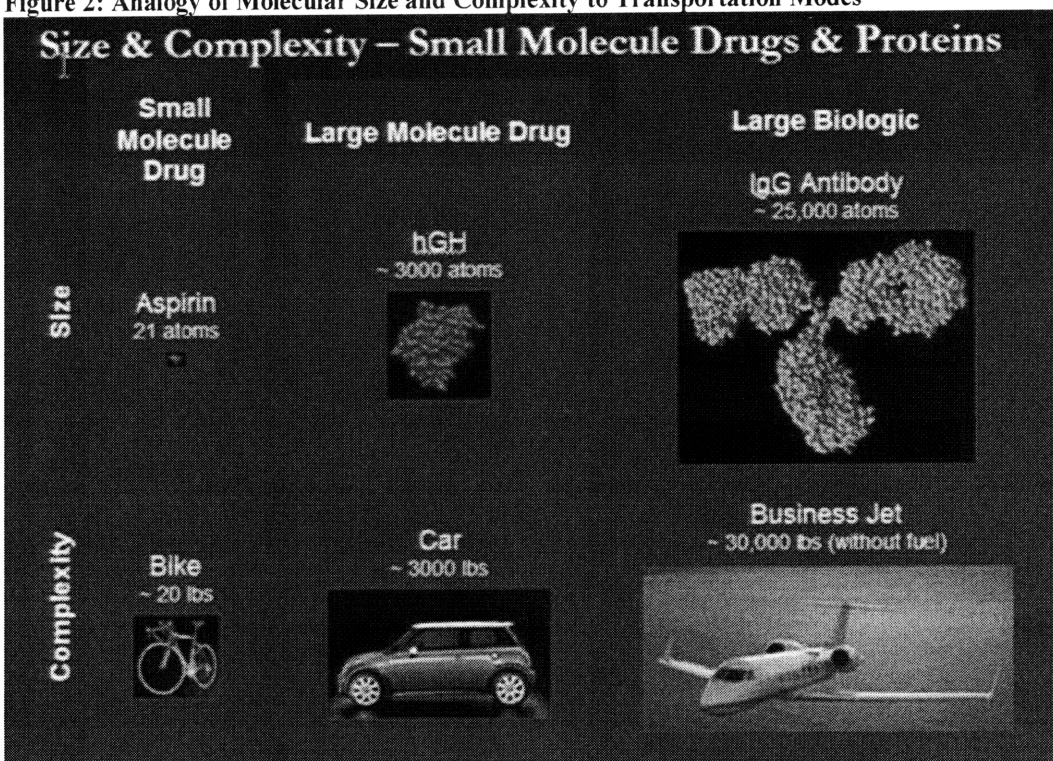
sequences that the human body adversely reacted to. The product Antibody-A is an example of a MAb that is manufactured by Amgen. Further discussion of this product's manufacturing process is in the next section.

Biopharmaceutical and pharmaceutical processes are designed to be completed in discrete batches for traceability and control purposes of the products. Many of these requirements for traceability are set forth by government regulatory agencies such as the Food and Drug Administration (FDA) in the United States in current Good Manufacturing Processes (cGMP). The pharmaceutical industry operates under severe time pressure to produce products as soon as the product is approved for sale by the FDA because of a limited patent-protected time period (as a monopoly) before generic competition can begin. Biopharmaceutical manufacturing and process development groups must balance the pressure of time-to-market and designing a cost-effective system so that the process submitted to regulatory bodies is robust enough for both goals, since process changes are so hard to enact.

Biopharmaceutical manufacturing processes are highly complex processes, sensitive to many factors. One cause for the complexity of the manufacturing process is the size and complexity of the active molecules themselves. An analogy in transportation machines is depicted below in Figure 2, with the size of molecules given by the number of atoms in each molecule. In fact, slight differences in chemical structure resulting from changing manufacturing scale can be a cause for regulatory agencies to prevent approval of a product that is essentially the same as an approved product, as evidenced by Genzyme's Myozyme<sup>®</sup> difficulties (Wallack, 2008). Another cause for complexity in biologics manufacturing is the possibility of microbial contamination and other risks that can potentially fail the strict requirements for purity, potency, and safety of biopharmaceutical products.



Figure 2: Analogy of Molecular Size and Complexity to Transportation Modes<sup>1</sup>

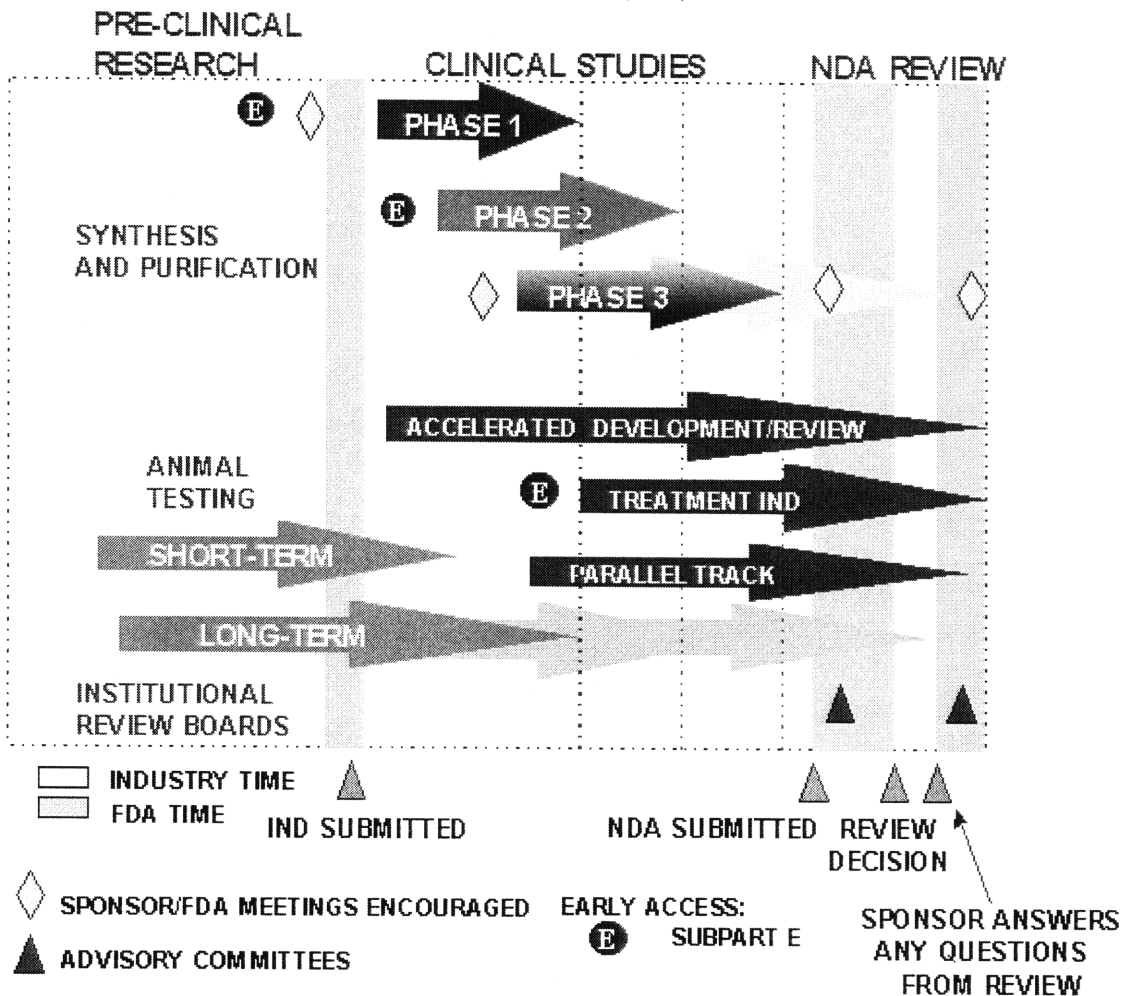


The biopharmaceutical business model is one of high risk and high reward. Significant resources are devoted to discovery of the biopharmaceutical, development and validation of the manufacturing process, clinical trials to test the biopharmaceutical for safety and efficacy in the target patient population, all in order to provide sufficient justification to several governmental regulators to sell a product. This process of product development entails several parallel approval stages by regulatory bodies. The Food and Drug Administration (FDA) regulates the marketing of biopharmaceuticals and uses a phase-based approach to drug approval within the United States. This approach is briefly summarized and depicted in Figure 3 below (Food and Drug Administration):

- Preclinical Research – discovery, animal testing for dosage, and delivery system development
- Phase 1 – small scale healthy human testing
- Phase 2 – test against targeted disease in small number of patients
- Phase 3 – large scale study on effectiveness and side effects

<sup>1</sup> <http://www.gene.com/gene/about/views/followon-biologics.html>

Figure 3: Pharmaceutical New Drug Approval Process (FDA)



Another risky aspect of the biopharmaceutical business is the production capacity planning decision for products that are in a company's development pipeline. Since the opportunity cost of not meeting anticipated market demand for a new drug or biologic is astronomical, ensuring supply through excess capacity is an operational priority (Haupt, 2005).

Current challenges facing the biotechnology and pharmaceutical industries include:

- Research productivity has been shown to be declining for the pharmaceutical and biopharmaceutical industries as well (Pasanek, 2008).
- Competition from biosimilars (bio-generics) is a growing specter to innovative biotechnology companies such as Amgen (Amgen, 2005).

## **2.2 Manufacturing Background**

Manufacturing of a biopharmaceutical product is a highly complex biological and chemical process. Much of the skepticism encountered during implementation of Lean in the biotechnology setting is derived from the perception that the peculiarities of biopharmaceutical manufacturing make it impractical to implement, as opposed to other industries such as automobile manufacturing, where Lean originated (Womack, Jones, & Roos, *The Machine that Changed the World*, 1990).

Biopharmaceutical processes are designed to produce batches of product for traceability and control purposes. In general, the bulk manufacturing (batches of large volumes of liquid products not yet divided into individual syringes or vials) can be broken down in two major phases: upstream and downstream processing.

- In upstream processes, the product of interest is produced by the organism or cell that was genetically engineered for that specific purpose. Upstream includes the expansion, or proliferation, of the cells from a small starting volume and concentration to a much larger quantity of cells that can produce the protein of interest in sufficient quantities for the customer's needs. Therefore, upstream can be considered production of the cells needed and also the final production of the protein of interest. Media containing nutrients are feedstocks as well as the starting "seed" or volume of cells from a working cell bank. Expression of the genes to produce the product of interest occurs as the last step before isolation of the product in downstream processing.
- Downstream processing encompasses all of the processes needed to isolate and purify the protein or compound of interest in a sufficiently pure, concentrated, and physical state. These processes include centrifugation, various types of filtration, and various types of chromatography. Care must be taken to minimize damage to the product, maximize yield of the product, and prevent introduction of any foreign unwanted substances. The bulk drug substances (BDS) is then ready for the fill and finish processes to package and label the product into vials or syringes.

After BDS are produced, they are further processed into the final dosage form for sale and distribution, typically pre-filled syringes, vials of liquid, or vials of lyophilized (freeze-dried) product. In the case of Antibody-A, pre-filled single-use vials constitute the final dosage form, or final drug product.

Manufacturing technologies for biotechnology products have evolved and expanded since the beginning of genetic engineering, as was alluded to in Section 2.1. Product discovery and design result in technological advances. For example, prokaryotic (bacterial) and simple eukaryotic (yeast) mediums were used in early biotechnological products, more complex proteins required the use of mammalian cell cultures, which introduced a whole host of new technological challenges (Blanch & Clark, 1997). At present, new production technologies such as Process Analytical Technology (PAT) and Quality by Design (QbD) are also being explored to reduce the complexity and improve control of biopharmaceutical manufacturing (Davies, November 2006) (Kourti, 2006). Additional technologies are being developed to push the boundaries of biotechnology manufacturing. For example, disposable equipment alleviate the challenges associated with the stringent needs for sterility (Xcellerex) and modular designs for clean room facilities are being touted for faster less costly engineering validation (AES Clean Technology, Inc.).

#### *Amgen and Biotechnology Manufacturing*

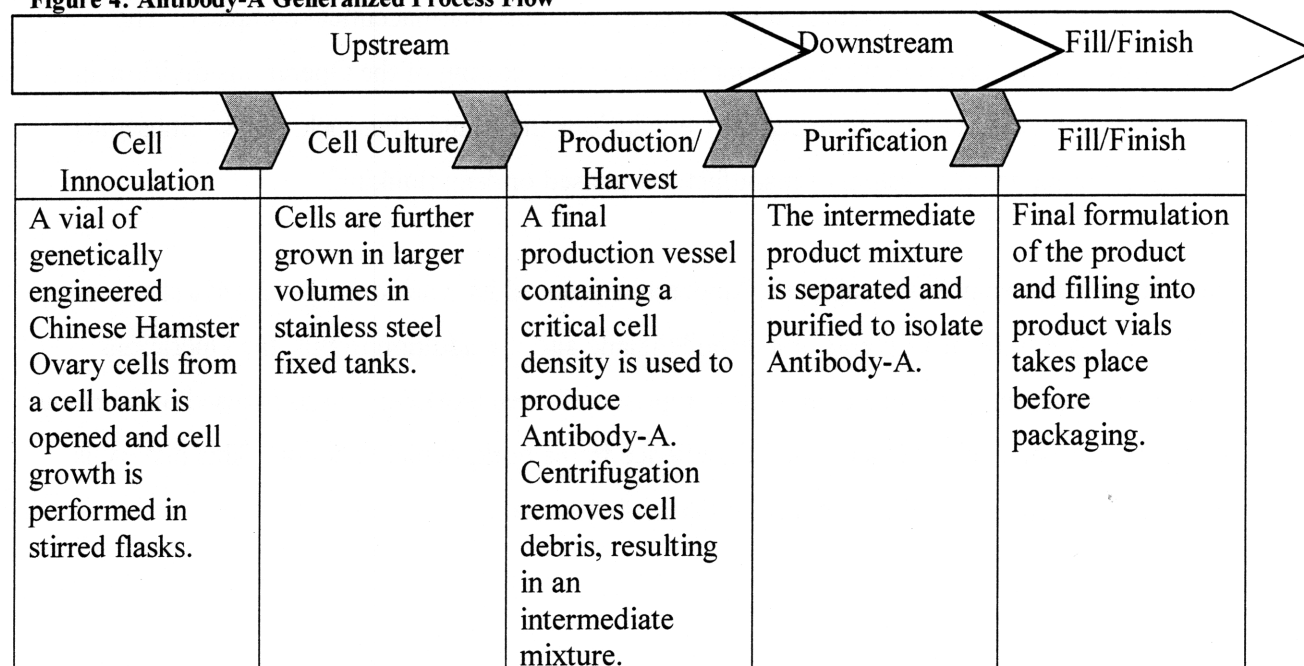
Amgen was established in 1980 as AMGen (Applied Molecular Genetics). Amgen's role in the development of biotechnology manufacturing has been highly influential and the company is considered to be a pioneer of the industry. Their first major product Epogen® (Epoetin alfa) was a breakthrough product in biotechnology. Their second major product Neupogen® (Filgrastim) was also one of the earliest biotechnology products. Both were blockbusters (reaching over \$1 billion in sales per year). Amgen's current product line spans small molecule pharmaceuticals to large complex biopharmaceutical proteins and antibodies, making it a diverse manufacturer of human therapeutics.

Amgen's manufacturing facility in Fremont, CA was acquired in 2006 and manufactures Antibody-A. The facility was designed for manufacturing capability to produce BDS

(mammalian cell culture and purification) as well as final dosage form with Fill and Finish equipment. The site was also undergoing a major capital expansion project to increase manufacturing capacity (Leuty, 2007). This facility was chosen by the Operations Improvement team as a focus area because the site lacked a dedicated industrial engineering (IE) resource and previous work by the team had identified significant potential for improvement.

Antibody-A is produced using mammalian cell culture technology for its upstream processes. The downstream purification processes use a series of filtration, centrifugation, and chromatography technologies. The production of this product follows a generalized process flow depicted below:

**Figure 4: Antibody-A Generalized Process Flow**



Buffer preparation, which is described in this thesis, is the process of producing buffer solutions, which are critical components that are vital to successful separation and purification of Antibody-A. This process involves producing aqueous solutions of different compositions and pH designed for use in specific chromatography steps (Aldington & Bonnerjea, 2007).

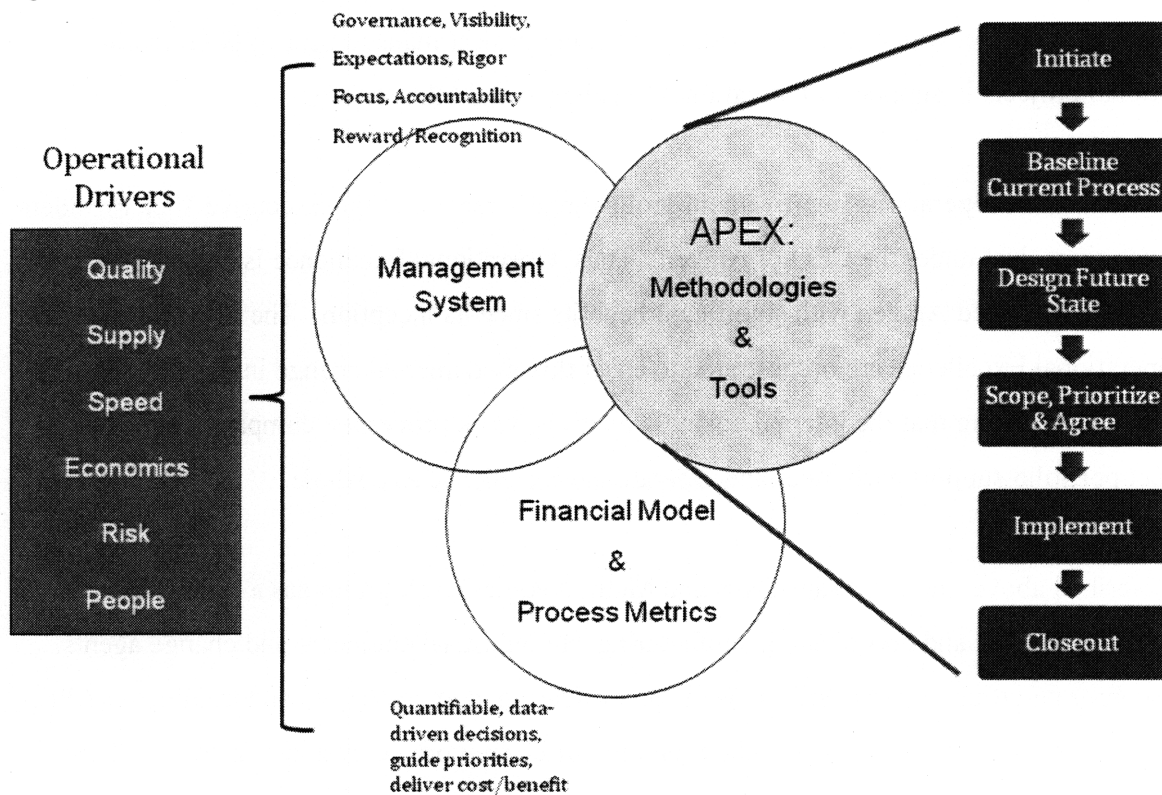
### ***2.3 Organization of Operational Excellence at Amgen***

Amgen faced many challenges in its business in 2007. In short, Amgen's anemia franchise, which is composed of Aranesp and Epogen, and makes up a large proportion of Amgen's sales and profits, had a drop-off in revenues. This drop-off was prompted by regulatory actions to lower reimbursement in the United States and lower doses of these drugs, because of safety questions that were raised from clinical trials (de Aenlle, 2007). Adam Villa also provides an excellent discussion of Amgen's company history and development leading up to its Operational Excellence efforts (Villa, 2008).

To address the challenges that Amgen faced in 2007 Operations embarked on an Operational Excellence initiative aimed at reducing the costs of Operations in order to continue investing in its R&D pipeline of future products, a vital activity for a biopharmaceutical company. The initial results of the program were a comprehensive restructuring of the Operations division and key decisions to halt investment in capacity expansions in Ireland. (Pasanek, 2008) Subsequent goals are to implement a system of manufacturing based on lean thinking.

Once the restructuring was completed, Amgen had reduced its workforce by 12-14% (Pasanek, 2008) and closed one of its plants at its Rhode Island site. In addition to this, the Operations Improvement group was created and was comprised of three working groups focused on working on the three aspects of the Operational Excellence framework, depicted below. This history is important to organizational acceptance of OpEx/APEX/lean.

**Figure 5: Amgen's Operational Excellence Framework**



The APEX Tools and Methodologies work group, where this internship resided, is focused on developing the APEX methodology or framework and acting as additional capacity/capability for projects needing the help. The size of this group is small relative to the aggregate of the working groups within Amgen's manufacturing network that have been tasked with execution of continuous improvement. This group is focused on supporting the several process improvements happening throughout the manufacturing network.

The Business Analytics work group develops and maintains operations metrics for the network, focusing on the Financial Model and Process Metrics piece of Operational Excellence. It is also working on analyzing capacity utilization and rationalization/longer-range planning of the assets of the manufacturing network.

The Management System piece of Operational Excellence is made up of the Program Management Office, which is tasked with maintaining project management of large cross-functional projects in support of Operational Excellence and other efforts.

The leader of the Operations Improvement group directly reports to the Executive Vice President of Operations, just under the CEO of Amgen. Thus, Operational Excellence is high profile and has already provided Amgen with significant benefits since its inception. The three components of Operational Excellence are orchestrated to enact this fundamental change in the way of business by ensuring that the internal business controls, work processes, company culture, and project portfolio support each other and Operational Excellence as a whole.

As described above, the corporate Tools and Methodologies work group has a central role intended to support and coordinate manufacturing site industrial engineers and change agents. As a corporate group, it had relied on hands on evaluation, demonstration, and training on APEX at various sites within the network. The Fremont buffer prep project resulted from one of these interactions. In the end, implementation of the plans and recommendations is the responsibility of the plant to prioritize among its workload to execute and capture benefits.



## Chapter 3: Buffer Preparation Process Improvement

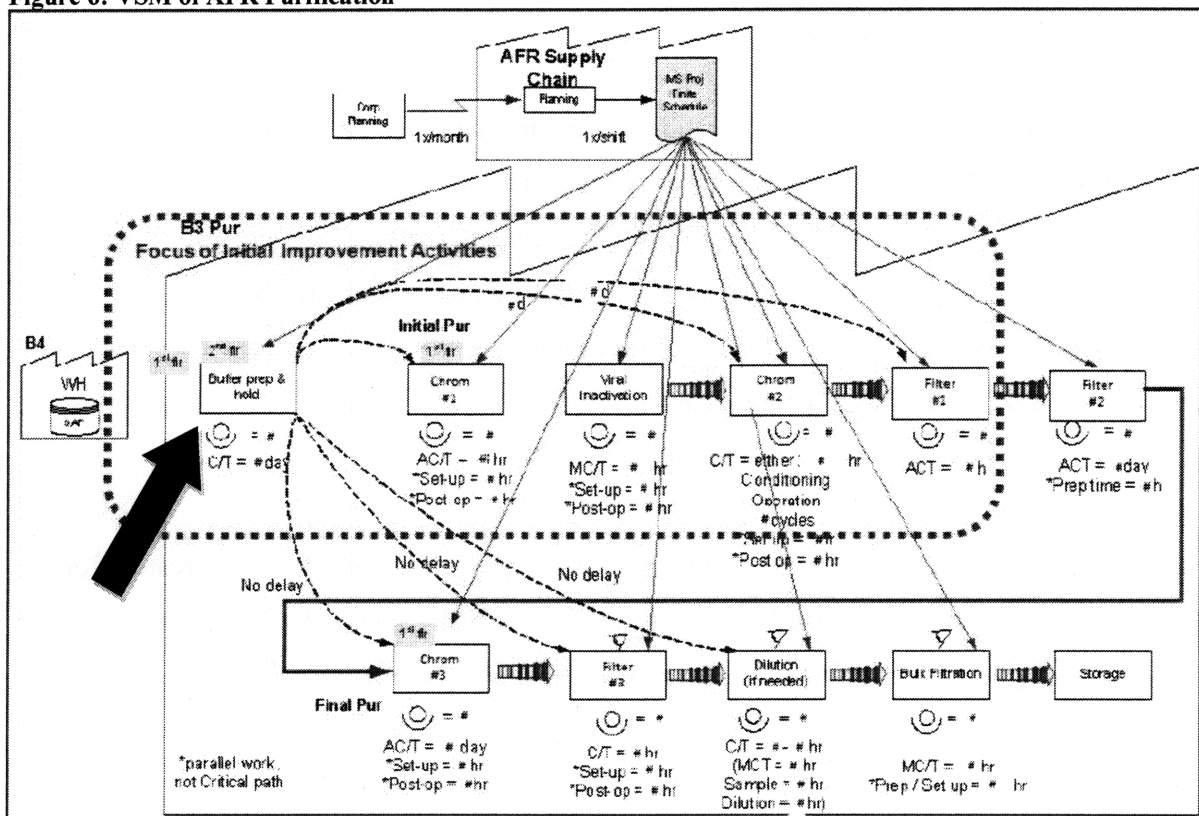
The buffer preparation process improvement project is described according to the APEX sequence of steps. This project was one of many other operational excellence projects at AFR.

### 3.1 Initiate

As discussed by Adam Villa, Amgen Fremont participated in the initial implementation activities led by Operations Improvement. These activities were aimed at assessing various options to improve resource utilization in anticipation of increasing demand for Amgen's products and/or introduction of additional products to be manufactured to the facility.

Value stream maps of the cell culture and purification processes were created during the initial visits. The purification value stream map is reproduced below and as discussed by Villa, the buffer prep process was identified as a process bottleneck for purification.

Figure 6: VSM of AFR Purification



After the team presented its findings and there was agreement to further analyze the opportunity at buffer prep and buffer hold (buffer storage prior to usage), the initial priority was for direct process observation. Buffer preparation cycles repeat throughout the purification process so it was possible to observe multiple operating scenarios that occur for buffer preparation. The focus of the direct observation visit was to find further opportunities for 5S organization of the buffer prep workplace in order to improve efficiency, to validate a process map created for buffer prep, and to find improvement opportunities to shorten the buffer prep cycle and/or reduce the amount of labor effort involved.

Starting this particular effort required the involvement and buy-in of several parties. A stakeholder analysis helped to make sense of the multiple relationships that need to be maintained. One of the key findings from the stakeholder analysis was that the AFR site personnel – manufacturing associates, supervisors, and QA personnel – required the most buy-in and required the most effort to increase support.

### ***3.2 Baseline Current State***

To effectively approach the buffer preparation process from an improvement standpoint, additional characterization of the process was needed. The AFR Downstream (purification) group did not keep cycle time metrics for the buffer preparation process. Microsoft Project was used by the Planning/Scheduling group to track production progress of each batch of bulk Antibody-A being manufactured. Project is a useful tool for project management; however, its application to scheduling manufacturing can be cumbersome and its value diminished as it is applied to a process that should be routine and repetitive.

Prior to the direct process observation, a Process Map for Buffer Preparation was created from the buffer prep Standard Operating Procedures (SOPs) and SME interviews. It is depicted in Figure 7 below after being validated by direct observation of the process and SME input.



1. The entire process to produce one tank of filtered buffer ready to be used in purification often lasted longer than one 8-hour shift. A pattern emerged where a typical day shift operation for the buffer prep room entailed:
  - a. Assignment of operators from the purification team during the morning shift meeting. The assignment process seemed to lack structure: the supervisor typically asked for volunteers for specific tasks required that day such as buffer prep, running a chromatography column, or washing parts in the component prep room.
  - b. Two operators either continued the process of finishing a buffer from the previous shift or started a new set of buffers required for that day.
  - c. Value-added activities included: measuring and addition of solutes, pH measurement, addition of acids to adjust pH, and operation of equipment via a Human Machine Interface (HMI) terminal.
  - d. If starting a new batch, the process typically ended at the end of the working shift before the buffer was filtered and transferred to a hold tank
2. There were a myriad of issues causing delays and extending the buffer prep process over the course of the day:
  - a. Lack of urgency: some buffers, especially the ones used earliest in the purification sequence, are made well in advance of when they are needed.
  - b. Troubleshooting other processes.
  - c. Waiting due to lack of availability of support systems such as the Clean-in-Place (CIP) automated cleaning system used to wash the tanks and pipes in between batches.
  - d. Difficulty in working with some materials such as solid urea that tended to cake together into pieces that were hard to break apart.
  - e. Special causes: some equipment outages were caused by the capacity expansion project and re-qualification activities that were ongoing due to restarting from a shutdown.
3. The tenure of staff making the purification buffer solutions drove down the time to complete making a buffer. Staff with greater experience performing the task typically

had shorter preparation times. The value of experience was most apparent in the iterative loop of titrating the buffer to its target pH.

A preliminary opportunity list was formulated from the direct process observations. 5S efforts were already under way at the plant, starting at its component preparation (washroom and parts storage) area and the team planned to also organize the buffer preparation room using the 5S tools in the future. The buffer prep process was evaluated from the beginning when a decision was made to initiate a buffer batch until the buffer solution was transferred into a hold tank awaiting use in the purification process. The list of potential initiatives that we brainstormed is shown below:

**Table 1: Preliminary Opportunity List**

<b>Opportunity</b>	<b>Potential Benefit</b>
Implement Standard Work	Stability: tighter & lower cycle time (C/T)
Install Online pH Analyzer vs. Offline pH instrument	Lower C/T for pH meas. & titration steps
Optimize buffer transfer rate	Lower C/T
Optimize mix times	Lower C/T
Rationalize QS step	Lower C/T

Some of the proposed ideas require a significant amount of engineering development resources to implement. For example, at the time we did not understand the rationale behind some of the minimum mixing times prescribed in AFR's SOPs. From experience at other biotechnology manufacturing facilities where minimum mixing times were considerably shorter than the 30 minutes required by some AFR SOPs, we wanted to determine if there was any opportunity to shorten the prescribed time required. From this list, we contacted additional SMEs within AFR—process engineers, automation engineers, and maintenance workers. Some ideas were eventually dismissed—process validation documents and experiments during process development supported the long mixing times, which were ultimately caused by the tank geometries.

Since the direct process observation time was limited to one week of manufacturing and the scheduling of the buffer batching often shifted due to variation in the process and schedule, it was not possible to observe the full range of buffers that are made for a production run. Therefore, it was decided that the team access historical data that is recorded by the plant's control system and database.

The plant uses a fairly common system to record process data from its process control units, built by OSIsoft, Inc and called the PI System. These software tools allow the user to examine continuous data such as temperatures, pressures, tank levels and volumes from previously completed batches and in real time. Equipment and instrumentation tags from Piping and Instrumentation Diagrams (P&IDs) map to the equipment and instrumentation tags in PI. The software also records all operator entries into the control system, with each entry time stamped. Finally, another tool allows for compressed data to be exported to an Excel spreadsheet for a specified time frame.

#### *Data Collection Plan and Methodology*

A data collection plan is very important so that sufficient data are taken for a representative sample and so that the analyst does not waste time and resources collecting too much data. Our methodology for data collection was to find representative buffers for each family or similar group of buffers (typically, each type of buffer has various concentrations and/or pH's used at different points of downstream processing) so we did not have to characterize the entirety of the 17 buffers made at AFR. We leveraged the plant's automation and data acquisition tools to download discrete time-stamped operator input data, tank level data, and pressure data that are continuously recorded.

Out of 17 different buffer types, five buffers were chosen for a representative sample. These five buffers were chosen based on Amgen Fremont's own methodology of grouping the buffers for conducting mixing studies and process qualifications (tests to establish process parameters and to ensure the processes create reproducible end results given the range of process conditions). These five buffers represented the three major buffer "families": acetate (at high and low concentration), citrate (at high and low concentration), and urea buffers. Some of these specific

buffers were considered “worst case” with the highest concentrations and most stringent conditions, and they were used for the engineering analyses to establish minimum mixing times. Some simpler buffers that take a substantially smaller amount of time were then pooled into another group and statistics for that sample group were calculated for aggregate improvement predictions.

Availability of Antibody-A production history at the current scale was relatively limited. However, there were enough samples since the beginning of production to provide some indication of what the production cycle times looked like. The target of 20 batches for each buffer sample set was not met for some buffers because they are not made as often during the course of a production run (e.g. once versus maybe three times during a production run).

**Table 2: Buffer Prep Sample Set**

<b>Buffer Classification</b>	<b>Buffer Vol./ Tank Vol.</b>	<b>n</b>	<b>Why selected?</b>
High Concentration - Urea	~400L / 1500L tank	14	SME noted that dispensing step is highly variable, high concentration, titration
High Concentration - Citrate	~1550L / 3000L tank	20	Used as a worst-case buffer in mixing studies, high concentration, no titration
High Concentration - Acetate	~1500L / 3000L tank	15	Used as a worst-case buffer in mixing studies, high concentration, titration
Low Concentration - Citrate	~2500L / 3000L tank	20	SME noted as low difficulty buffer with fewer issues than others, no titration
Low Concentration - Acetate	~3000L / 3000L tank	20	Largest volume, requires titration

Since the buffer prep process caused purification processing to halt and wait for buffer solution availability, buffer preparation process cycle time was the primary metric targeted for improvement. Using historical data for base-lining the buffer prep cycle times was the first objective. Because there are various types of buffers, ranging in the amount and number of solute materials, total volume, and requirements for pH and conductivity, the cycle times were

expected to vary depending on the buffer type and volume. Below is a table showing how each of the various aspects of the buffer solution and its requirements can affect how quickly it can be made.

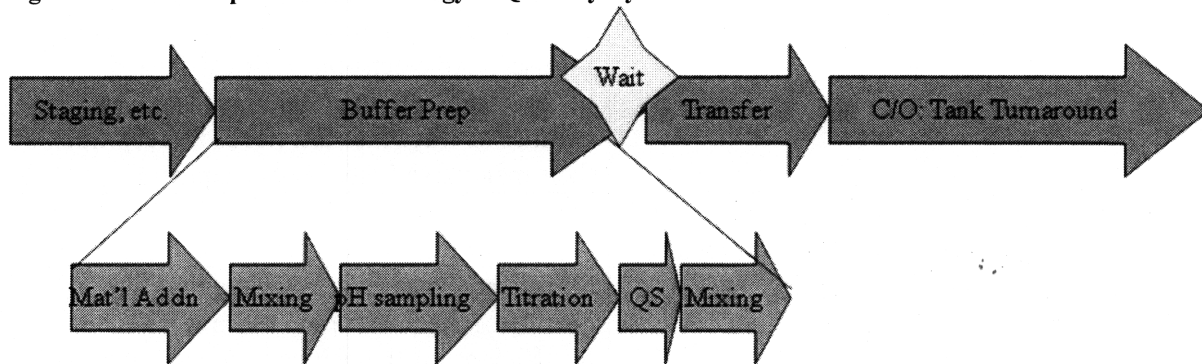
**Table 3: Buffer Prep Production Cycle Time Factors**

Buffer Requirement	Cycle Time Factors in Production
Material Charge & Total Volume	Water for Injection (WFI) inlet flow rate
	Material amounts
	Mixing parameters: speed, geometry of tank
	Material properties: concentration, solubility, particle size, etc.
	Buffer Filtering: tank pressures, filter specifications, equipment elevation
pH & Conductivity	Sampling method from tank
	Probe calibration for pH & conductivity
	Operator experience
	Specifications (large or small ranges)

From the process map depicted above, the buffer prep process was broken down into three discrete sections that follow linearly and are mutually exclusive within the process automation logic. These sections are: 1. Buffer prep, 2. Waiting before transfer, and 3. Buffer transfer. These three sections can be bracketed and cycle times quantified from the historical data. A diagram of the linear breakdown of the process is shown below. Outside of these three sections there are additional important activities, but precise quantitative cycle time data could not be produced for previously produced batches. These outside sections are pre-processing activities such as gathering and staging of equipment and materials, and set up of equipment. Also an outside process section is the post-processing activities such as cleaning in place (CIP), cleaning out of place (for small equipment and components), returning materials and equipment, and batch record reviews. It was noted to the plant that these “outside sections,” generally called changeovers (C/O), are also an important source of process improvements and similar approaches to improving these processes should be pursued.



**Figure 8: Buffer Prep Process Chronology to Quantify Cycle Times**



Process steps, (including non-quantified steps outside of process section) corresponding to Figure 8's linear diagram of the process, are described below along with brainstormed improvement opportunities. As one can see, the process involves several steps and requires many different tools and materials to be used and maintained.

**Table 4: Process Steps and Improvement Opportunities**

Staging, etc.	Opportunity
1. Operators must retrieve from 1 <sup>st</sup> floor shift change room and clean storage room: <ol style="list-style-type: none"> <li>Batch production record (BPR)</li> <li>Cart of verified clean equipment including:               <ol style="list-style-type: none"> <li>Funnel</li> <li>Pitcher</li> <li>Hoses</li> <li>Gaskets</li> <li>Clamps</li> <li>Pressure gauges</li> <li>Jumpers for wall piping</li> <li>Nalgene containers</li> <li>Filter housing</li> <li>Integrity (IT) Tester</li> <li>Test tubes</li> <li>Kimwipes</li> <li>pH and Conductivity standard solutions</li> <li>TeriWipes</li> <li>Gloves</li> <li>Filters</li> </ol> </li> </ol>	<ul style="list-style-type: none"> <li>A checklist and possibly a pre-arranged kit of materials will significantly reduce the wasted motion and time looking for so many items.</li> <li>Current efforts to improve part flow from the production floor through the wash room and to the clean storage room will help reduce wasted time searching for components.</li> <li>Standard work will efficiently deploy the two operators assigned to these duties.</li> </ul>
2. Verification of process equipment for	Stickers, placards, and equipment logs are used

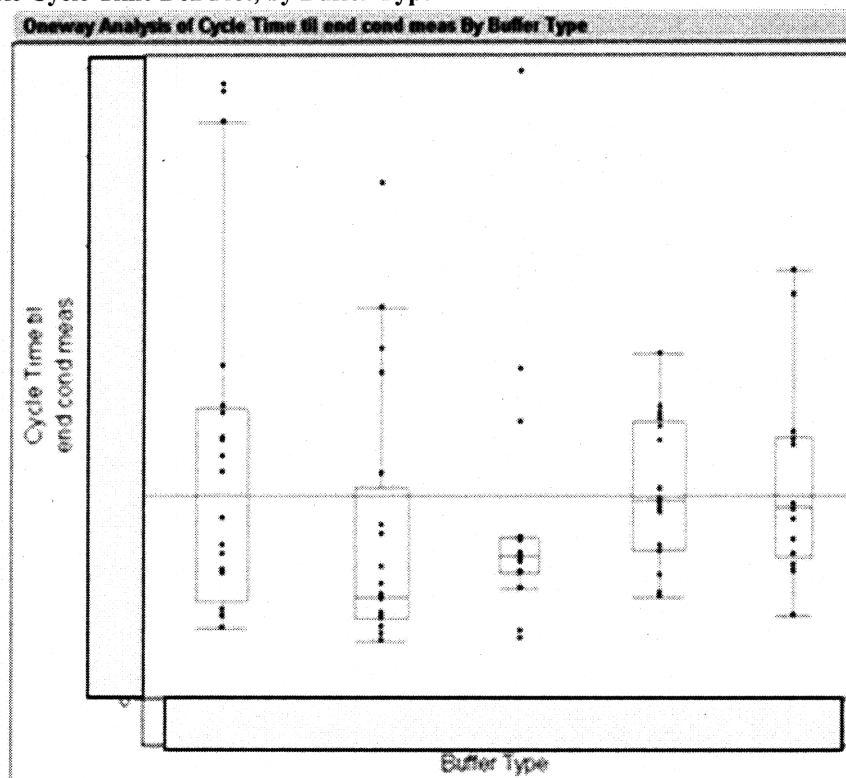
cleanliness and readiness to run	to update and signal equipment status of “in use”, “cleaning in process”, and “clean/ready for use”. An electronic verification and notification system would help reduce the number of ways the staff needs to keep track of their major fixed pieces of equipment.
3. Verification of material availability and placing warehouse orders as necessary	
4. Pallet movement, dispensing, and recording materials.	Sometimes, materials in the staging area outside of the buffer prep room were insufficient for the planned run, and materials needed to be ordered from the warehouse. This is a symptom of incongruous flow and can be helped by implementing a kanban, or pull, system.
<b>Buffer Prep</b>	
1. Initiate recipe on HMI	Throughout the process, there were pervasive double entry of data into the BPR and the HMI process control computers. This is a waste of operator time and introduces the possibility of errors. Electronic batch records from the HMI would help to remove this waste.
2. Start WFI flow	One tank’s WFI flow rate was substantially lower than others. May be an issue with a flow restrictor.
3. Dispense & add solute materials, verify input into BPR & HMI	Pre-weighed kits of solutes were in large demand from the operators. Some materials such as urea were hard to break apart to effectively measure and dispense.
4. Mix for a minimum prescribed time	Because this is a minimum requirement, there are inconsistent lengths of time an in-process batch of buffer is allowed to mix. Sometimes, operators are sidetracked, reassigned to other tasks, or simply lose track of when the next step can begin.
5. Measure pH (as required by SOP): a. Sample from tank b. Calibrate pH meter c. Measure sample d. Record	Install and implement in-line pH probes into the pre-existing wells. This would provide measurements without having to take samples and help reduce the titration time.
6. Adjust pH (“titration”) a. Calculate volume of per SOP b. Measure desired aliquot c. Add aliquot d. Record addition e. Mix	Implement standard work for this process. Investigate in-line probe implementation—fittings exist on the buffer tanks to use this technology.

f. Perform Step 5 (Measure pH)	
7. QS – Add WFI to target volume of buffer.	Investigate reformulating the steps to produce the buffer to eliminate the final QS WFI addition to reduce time of liquid-liquid mixing.
8. Mix for a minimum prescribed time.	
9. Measure conductivity of buffer.	Investigate in-line probe for conductivity – see pH
10. Filter and transfer to holding tank.	
11. Changeover/Clean equipment.	Better scheduling and usage of CIP systems Part flow through cleaning should be investigated

Sources of process variation were also identified once the variations in cycle times were quantified. pH measurement and titration was a major source of prolonged cycle time. Material dispensing was a difficult parameter to quantify from OSI PI data because much of the work in measuring out materials could be done prior to starting the buffer recipe in the process automation. However, the time duration between initial water addition and the acknowledgement of all materials having been added to the vessel gave an indication of the variation involved. Mixing times extended beyond the minimum prescribed times due to a variety of reasons, including multitasking and shift changes. Also, operating conditions such as pressure during buffer transfer was found to cause variation in the speed in which a tank of buffer could be filtered and transferred to its holding tank. Finally, training and process aptitude from experience was a common factor affecting cycle times.

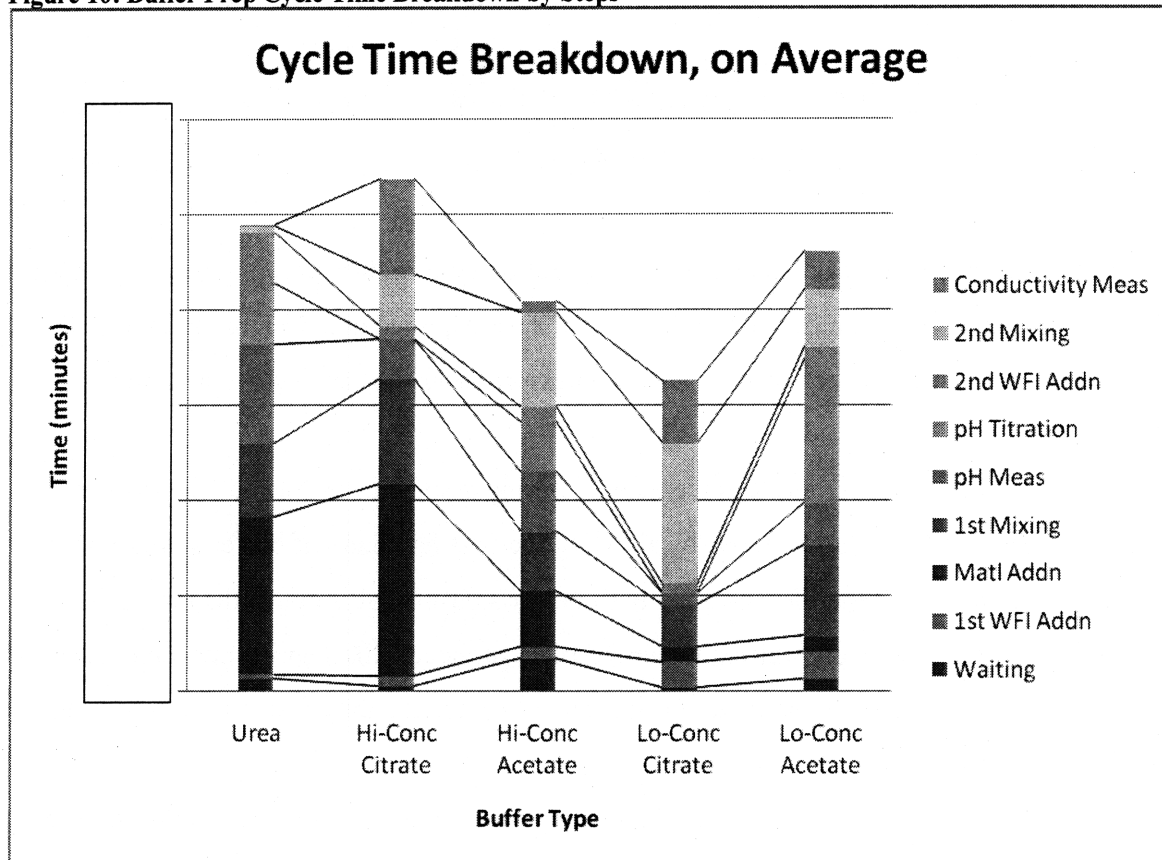
The sample cycle times of the five buffer classifications are depicted in a box plot shown below.

Figure 9: Sample Cycle Time Box Plot, by Buffer Type



It was observed that among the given different buffer types that were categorized, some buffers, especially those with minimal complexities (no pH adjustment/titration required) had much smaller amounts of cycle time variation and vice versa. Also, the breakdown of the buffer prep cycle time is dominated by different steps: e.g. material addition takes a significant portion of the time for difficult materials (urea) and for higher concentration buffers. The breakdown is shown below in Figure 10.

**Figure 10: Buffer Prep Cycle Time Breakdown by Steps**



One challenge of the analysis was to determine what, if any, were the special causes of significantly long step times. We found that special causes such as equipment breakdowns or outages are intended to be rare, but this did explain many recent points (especially because the facility was still undergoing many engineering upgrades and tests). In general, many long delays were not immediately attributable to a specific equipment outage. Some delays lasted through weekends when there was insufficient staffing or purification process need to keep the buffer prep process going. Some delays were due to unavailable tank space in the holding tank room. Most of these causes were determined by operator interviews.

The third section of the buffer preparation process is Buffer Transfer. It is described below:

Buffer Transfer Process Description:

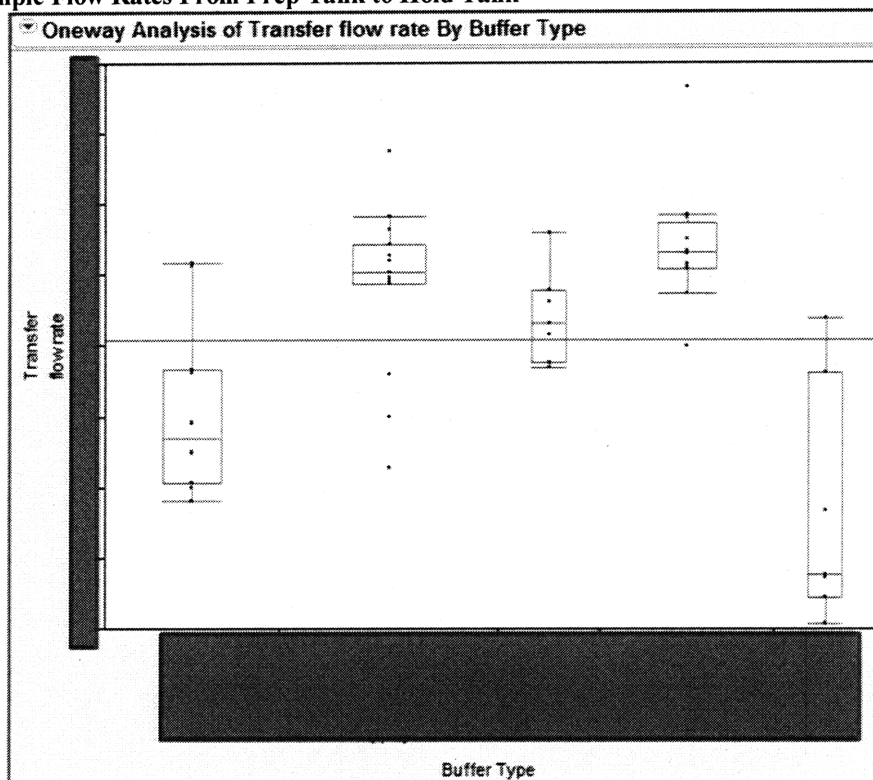
1. The automation prompts the operator to establish the connection via the transfer panel separating the buffer prep room from the buffer hold room, so that the prep tank is connected to the buffer hold tank via piping and valve manifolds. Some prep tanks are

restricted to a subset of the hold tanks that are available due to piping and valve limitations.

2. Additionally, a liquid filter is installed in the piping close to the inlet into the hold tank selected. This is a manual process where a clean filter housing must be installed and all fittings must be tightened.
3. Flow is initiated and maintained by a pressurization system that goes into the prep tank's air headspace above the buffer solution. Plant air is supplied at a design maximum of 30psig. A regulator is present to allow for pressure control by the plant automation system.
4. Initiating buffer transfer requires the manufacturing associates to "prime" the system, more specifically the buffer filter, by allowing the first few liters of buffer solution to flood the piping and the filter housing until buffer solution spills out of the top of the filter housing, effectively wetting the entire filter surface. This step is important because any air that is present on the filter surface removes filter capacity that is utilized during filtration and transfer.
5. Buffer flow is maintained by controlling the pressure of the headspace of the buffer prep tank. Initially, the buffer prep automation recipe sets the pressure set point to 12psig. Procedures and historical practice allow for the associate to adjust the pressure up or down, and SME interviews as well as previous data from the OSI system show that operators have adjusted the set point of the pressure to pressures reaching 18psig. As pressure is increased, flow is expected to increase, as shown in the filter flow curves reproduced below in Figure 12.

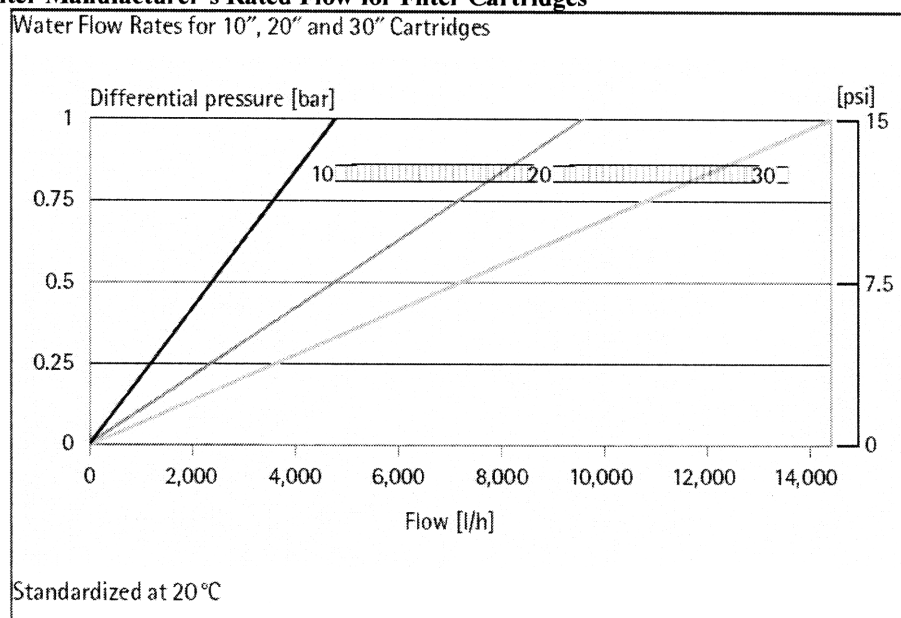
The approach taken by the team to evaluate the process was to quantify the flow rates of buffers from the prep tank to the hold tank, and then compare these flow rates to the expected flow rates given by the buffer filter manufacturer. Table 5 shows the calculated flow rates (as a percentage of predicted) for each buffer type and Figure 11 shows the distributions of flow rates by buffer type.

Figure 11: Sample Flow Rates From Prep Tank to Hold Tank

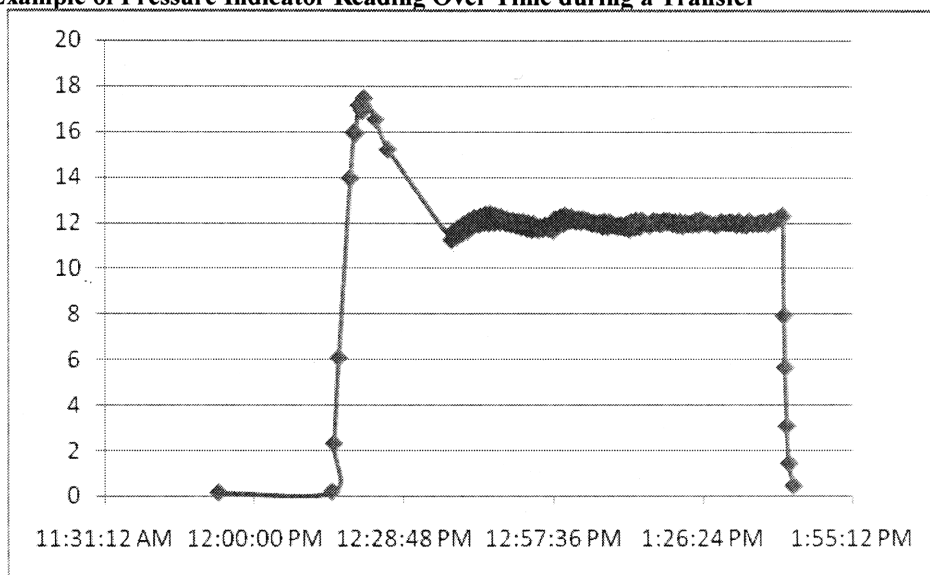


The filter manufacturer sets expectations for the flow rate in its specification sheets via filter flow curves shown below (Figure 12). The plant used two sizes of filter cartridges, depending on the buffer. For example, a highly concentrated buffer would use a larger filter with greater surface area to maintain a reasonable throughput through the filter, whereas a low concentration buffer would typically use a smaller filter because it provides adequate flow. At 12psig (or 0.83bar-gauge), the expected flow rate estimated to be approximately 66 L/min for the 10-inch filter (or 4000 L/h, or 6667 L/m<sup>2</sup>h). There is some loss in efficiency to be expected, because these solutions are not pure water and because the temperature of the water may not be exactly 20°C (Innes, 1956). For low concentration solutions, though, the flow curve should closely approximate the expected behavior because these solutions are the closest to pure water out of the other buffer solutions and the process is completed at room temperature. Finally, pressures at the prep tank were not completely constant as read from the pressure indicator, due to the dynamics of the process (see Figure 13).

**Figure 12: Filter Manufacturer's Rated Flow for Filter Cartridges**



**Figure 13: Example of Pressure Indicator Reading Over Time during a Transfer**



Linear regression of the transfer flow rates of each buffer using transfer pressure as a predictive parameter did not provide any useful conclusions—the maximum R-squared parameter out of the buffer types was 40%. Addition of additional explanatory variables such as fluid composition (material), temperature, pressure at the filter face, time since starting flow, and wetted filter surface area should improve the predictability of flow rate.

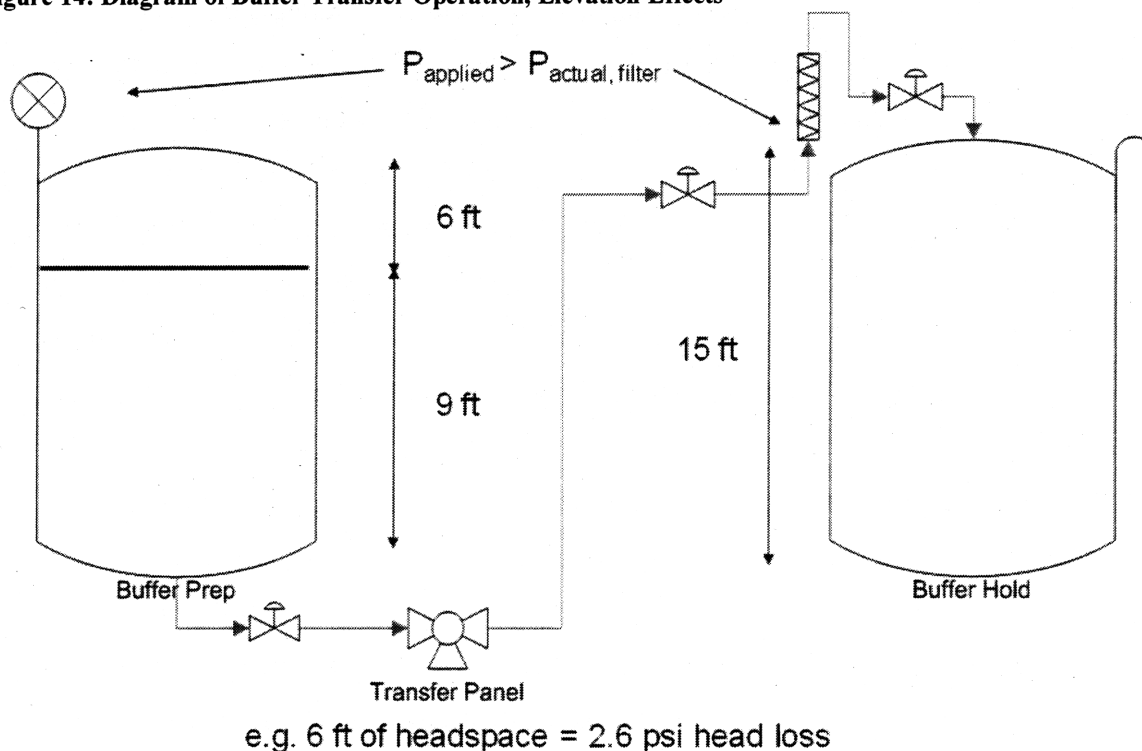


Using pressure data, tank level, and time data, the actual flow rate versus the expected flow rate was established for every batch in the sample set as a better way to measure buffer transfer performance. First, we assumed no pressure losses from the prep tank to the filter face. In reality, there is some pressure loss from the measurement at the tank's pressure gauge to the filter face. These pressure losses come from frictional losses through piping, valves, and connectors, and also from elevation changes (estimated at 2.6psi) as depicted in the figure below.

**Table 5: Filter Flow Rate by Buffer Type**

Buffer type	Avg % E(flow rate), no pressure loss	Avg % E(flow rate), assuming 3psi loss
Hi-Conc Urea	23%	29%
Hi-Conc Citrate	11%	14%
Hi-Conc Acetate	39%	51%
Lo-Conc Citrate	48%	63%
Lo-Conc Acetate	53%	70%

**Figure 14: Diagram of Buffer Transfer Operation, Elevation Effects**



### **3.3 Design Future State**

This phase of the APEX methodology, Design Future State, encompasses identifying many possible steps and targets for the process under consideration. This phase is primarily when process improvements are formulated by the team. This may involve generating what the future state VSM would look like, simply listing process improvement projects that have been brainstormed, and/or re-designing room layouts to facilitate improved flow in manufacturing.

#### *Standard Work*

Based on the observation of the absence of Standard Work, it was suggested that the plant commence the improvement opportunities by first standardizing their processes to establish the best practice in manufacturing a buffer solution. This activity is expected to produce a number of changes as discussed below:

1. Improve cross-shift communication and involve operators. During the process of establishing Standard Work, the various teams of associates who produce buffers will have to communicate with one another when establishing an agreed upon Standard Work document. This will start with thoroughly understanding the specific procedures that are used to complete the preparation of a buffer (including estimated times, contingency procedures, etc.). Efforts to improve the shift change information hand-off procedure were starting by improving the communication boards in the shift change room to show up-to-date equipment status rather than ad hoc verification via radio during shift change meetings.
2. Promote a habit of problem solving tied to operating performance. Once a standard is established among the manufacturing team, including expectations for task and step durations, multitasking/nesting of steps, and overall goals for the buffer prep process, one should not expect perfect adherence immediately. The first few times the process is run with Standard Work, unexpected circumstances will surely arise that prevent the team from reaching its goals. Therefore Standard Work will expose these circumstances that normally would be worked around or ignored when no expectations are set. In order to work toward adhering to Standard Work, the team must start the process of problem solving. There are many ways to solve problems, such as asking the Five Why's to arrive

at the root causes of problems, or more generally the Deming Cycle to steer the team toward its goals.

3. Establish tracking of process metrics. If buffer prep cycle time is a key metric and buffer prep speed is a key enabler to improve the Amgen Fremont factory, the cycle time should be measured and tracked. At the time of this internship, it was not measured by the manufacturing team. The reporting capability of their process control system was used only to verify completion of batches, but not the time duration to complete those batches.
4. Reduce process variation. The manufacturing team understood holistically that there was variability in their buffer prep process, that unexpected unavailability of equipment or materials, other priorities on the manufacturing floor diverted attention to the process, and uneven distribution of process knowledge contributed to differences in cycle times. However, the team did not have the data to see the degree of variability that was present in their process, and how this variability caused delays in the rest of the plant. Therefore, once the human element of the process is standardized and expectations are set, it is expected that cycle time variability will drop precipitously.
5. Reduce errors and uncertainty. Training to operate the processes in the biotechnology plant is comprehensive and vigorous, but imperfect. Little emphasis was given on how productive one should be, or how a team should organize tasks along a timeline. With a Standard Work document, with details on the “one right way” to execute a process, the manufacturing team will be better equipped to flawlessly execute their processes. Associates will understand what their role is, what the expectations are, and what methods to follow. This result will be felt most in the buffer titration step of the process, as discussed below.
6. Reduce cycle times. Finally, as the skewed right distribution of cycle times is compressed toward the target, the mean time to complete manufacture of a buffer will shorten. This will provide the plant with added flexibility to complete the remainder of their workload and will free up the amount of labor needed to accomplish purification of product.

A visualization of what standard work can do to improve operator utilization is shown below.

Actual standard work sheets would provide each operator in her designated role a specific list of

tasks along with the target times. It could also be aligned with 5S efforts with the expected physical process flow of the operator, equipment, and material in the processing room.

Figure 15: Buffer Prep Standard Work Visualization

Time	Process	Operator 1	Operator 2	
10		Inspect tank, BPR	Retrieve clean equipment, tools, filters, etc.	
20		Verify material avail, prep scale		
30	Initial WFI (2000L @ 85 L/min = 23.5 min)	Start recipe/WFI	Verify clean tank	
40		Ensure pH/cond probe & solutions ready		
50				
60		Verify wt & addition	Verify wt & addition	
70				
80	Material Addition (50 min)	Standardize pH probe	Dispense next material	
90				
100		Verify wt & addition	Verify wt & addition, start mix	
110		Retrieve acids & ppe		
120	1st Mix (30 minutes)	Pre-measure acids		
130			Prep sample collection tubes, etc.	
140	pH measurement (20 min)	Retrieve sample, verify mix		
150		Verify pH meas	Measure pH	
160		Add 1st acid vol		
170		Retrieve sample, verify pH	Measure pH	
180	Titration (assumes 3 acid additions)	Add 2nd acid vol		
190		Retrieve sample, verify pH	Measure pH	
200		Add 3rd acid vol		
210		Retrieve sample, verify pH	Measure pH	
220	QS		Prepare cond meas	
230		Start mix		
240				
250	Final Mix (30 minutes)		Free (50 min)	
260				
270	Meas cond'y (20 min)	Retrieve sample, verify mix		
280		Verify cond meas	Measure conductivity	

Hands-on work or verification

Free to multitask

BP Process, Delta V running

### *Running the Transfer/Filtration Operation at Higher Pressure*

The third quantifiable section of the process, buffer transfer, had much room for improvement. As shown in the previous section of this chapter, the maximum achievement of theoretical flow rate through the buffer filter was 70% of the expected filter flow curve value, assuming some frictional and elevation-related pressure losses. While there are many reasons why only a percentage of the theoretical flow rate is achieved, there are some ways that the operators can improve performance. The causality and opportunity analysis is shown below:

**Table 6: Filter Flow Improvement Analysis**

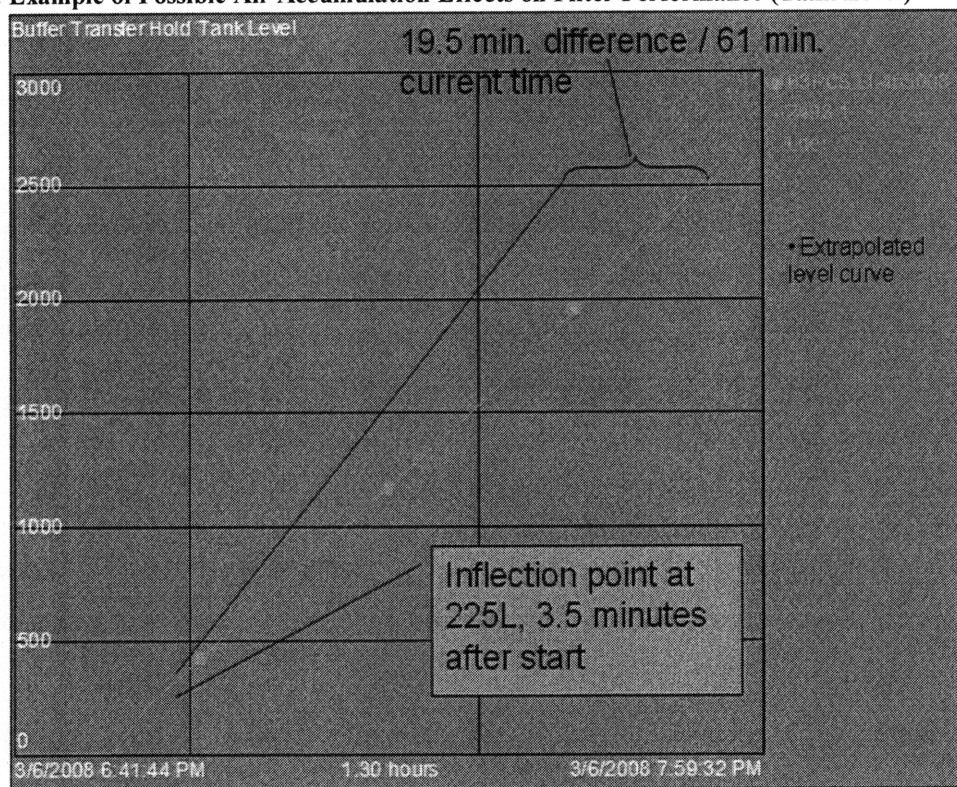
<b>Hypothesized Cause of Underperforming Filtration Flow Rate</b>	<b>Within Control of Operators?</b>	<b>Improvement Opportunity or Countermeasure</b>
Material – highly concentrated solution viscosity reduces flow rate	No, this is part of the formulation of the buffer.	None.
Pressure Control/Setting – pressure at the prep tank driving fluid transfer can be reduced by the operator	Yes	Increase the pressure at the prep tank up to the prescribed maximum operating pressure of the filter.
Air Within Filter Housing – less filter surface area is utilized	Yes	Improve filter priming procedure to minimize air bubbles

The team focused on the two factors under the control of operators. First, it was suggested that the pressure in the process automation currently set to 12psig be increased. Three possible limiting factors need to be defined for this pressure increase:

- The strength of the filter membrane: rated at 75psid differential pressure. An analog differential pressure gauge at the filter housing can be observed to establish the new tank pressure set point.
- The pressure rating of the tank and piping: the tank allows a maximum of 45psig.
- The clean plant air supply used to pressurize the prep tank. From interviewing plant engineers and maintenance mechanics, the maximum air supply pressure is 30psig.

A reasonable new pressure set point given the above constraints would be 25 psig (allowing for some inefficiencies of the air supply if there are multiple demands for the system). A second suggestion to optimally utilize the filter is to improve the priming procedure. Operators currently prime the filter by allowing the entire filter housing to be flooded with the first few of liters of buffer and then start the filtration and transfer operation. However, the historical data show evidence in some cases of deteriorated filter performance after just a few minutes and several hundred liters. The figure below is reproduced from buffer hold tank level indicator data. An “inflection point” is shown where the rate that the tank is filled suddenly decreases 3.5 minutes and 225L into filling the tank. This can possibly be a result of inaccurate level indicator readings at low tank levels, but the team suggested that a second priming procedure might increase the effectiveness of the filtration process.

**Figure 16: Example of Possible Air Accumulation Effects on Filter Performance (Tank Level)**



### *Implementation of Online pH Monitoring*

The pH measurement and titration procedures were found to take up significant portions of the buffer cycle time (from 28% to 42%) where those steps were required. Additionally, the variation, or spreads, of those step times were very large. Therefore, this part of the buffer prep process warranted significant attention for improvement.

First, the team attempted to identify the root causes of why these two steps were so problematic. From the operator's perspective, the cause was apparent—some operators have better skill with the pH probe calibration and operation, and some operators with more experience have greater confidence in performing the titration procedure. From the direct observations, the first point about using the pH probe was validated. Delays sprung from multiple attempts to measure the pH of a sample and the issues with the pH measurement process were identified below:

1. First, a sample from the bottom of the prep tank was required. This required the operator to gather the appropriate sample vessels and transport the sample from the lower level of the buffer prep suite to the workspace on the upper level where the pH probe was located.

2. Ideally before the sample is removed, the pH probe should have been calibrated (i.e. standardized) by the operator to the proper range of measurement. This requires identifying the right standard solutions, setting up the glass probe properly, and running the calibration procedure on the pH unit according to procedure.
3. Measurement of the sample pH required a subsequent check against a reference solution. This step was required to record a valid measurement. The check against a reference solution often resulted in problems where the operators attempted to troubleshoot the equipment, either trying to shake out bubbles in the probe, repeating a rinse with WFI, or swapping out the solution to a fresh bottle.

This troublesome pH measurement process is amplified by the repeated measurements required when adjusting the pH of a buffer (titration). According to the operators, titration is sometimes approached very cautiously by an operator with relatively lower experience for the fear of overshooting the target pH range and having to discard the entire buffer tank. This cautiousness manifested itself in adding smaller volumes of acid than calculated per the SOP. By adding smaller volumes, additional iterations of pH measurement, addition of acid, and mixing (for at least 15 minutes after addition) started to add up.

Second, ideas were generated to improve the process and procedures. Operators anticipated some improvement from 5S efforts to perhaps reconfigure the room so that the pH and conductivity probes are closer to the sampling point and better organization of the supply cabinet to ensure sufficient supply of sample containers and standard/reference solutions. To address the issues encountered during pH measurement, better training (perhaps collaborating with analytical laboratory colleagues on establishing best practices) and establishing standard work to ensure consistent use of the equipment were proposed as a first simple solution. The implementation of standard work to establish the proper amount of acid for pH adjustment by every operator is also expected to help reduce the variability of the titration process. Finally, a process technology solution that was proposed was to install and qualify the use of a tank-mounted in-line pH probe.

The ultimate solution that the team recommended was to pursue implementation of an in-line pH probe. This technology was piloted initially when the plant was started up, but lack of trust in

the probe measurements caused AFR to rely on the table-top off-line pH probe equipment, especially given the time pressures of establishing a validated manufacturing procedure prior to launching Antibody-A. The tanks already have the ports required and tie-ins to the process automation/data acquisition hardware that would allow use of on-line probes. The work required would be to experiment and qualify the best practice for calibrating, standardizing, and measuring the solution via the in-line probe. The anticipated benefits would be faster measurements by removing the sampling step, and faster titration by getting quicker feedback of the pH measurement as acid is added.

#### *Additional Opportunities*

Many additional ideas were generated to improve the buffer prep process:

- Opportunity to track key cycle times with available software; link to planning/scheduling and Operational Excellence
- Pre-measuring and kitting materials in the warehouse/dispensing area for each buffer so this work is done offline.
- Improved Raw Material handling when adding into the mixing tanks via a machine to grind down large chunks of solids into finer particles for faster mixing.
- Reduce the volume of buffer solutions made (they are currently made with an excess volume of roughly 20%) to minimize wasted WFI and solute materials as well as process time.

### **3.4 Scope, Prioritize, and Agree**

#### *Prioritization methodology*

Inevitably, many improvement ideas will come out of the analysis of the process and in specifying a desired future state. However, these ideas must be prioritized for time, effort, and resources required to implement them, since many companies have very limited resources devoted to process improvement. Amgen Fremont plant was responsible for completion of its own process improvements in order to increase the sense of ownership for these changes. Additionally, the fact that operators would implement the majority of improvements makes it



more likely that they would be widely adopted. Therefore, care was taken to think through the possible improvement efforts and prioritize them.

Three priority levels were created to categorize the improvement ideas. The first category was “Do First,” which means that there was minimal capital investment and the changes merely required shepherding them through the change control process in AFR. The “Do First” ideas all encompassed establishing standard work for the entire process and some changes in settings such as the buffer tank pressure during filtration/transfer and by establishing standard pH measurement and titration procedures. The second category in the prioritization scheme is “Investigate,” meaning some engineering effort and experimentation would be required to implement the idea. The idea in this second category is to install the on-line pH probe and eliminate the table-top pH instrument. Finally, the last category was “Investigate in High-Volume Situation,” where these improvement ideas were not expected to generate benefits as significant as the first two categories, or had significantly higher implementation costs. The ideas in this last category were to ensure inlet flow of WFI to a tank was brought up to the flow rate of other tanks and to potentially eliminate the second WFI addition (QS) in the buffer prep procedure. These were summarized in a table that was presented to the AFR Purification management and is reproduced below.

#### *Expected Cycle Time Improvement from Proposed Changes*

The team attempted to quantify the impact of these proposed improvements. Using the historical cycle time data, we set the 25<sup>th</sup> percentile of buffer prep cycle times to be the target for future batches moving forward. This improvement would be attributed mainly to Standard Work and amounted to 68.2hr/run or a 40% improvement in that process. No proposals were made at this time to reduce the waiting time between finishing a buffer solution in the prep tank and initiating filtration/transfer to the buffer hold tank. For the proposed increase to 25psig during buffer filtration/transfer, the improvement was estimated by the predicted increase in filter flow rate and with the total planned volume of the various buffers over the course of one purification production run. The total improvement was given by the predicted overall cycle time savings of almost 80 production hours over the course of one production run/batch of Antibody-A for the “Do First” category of ideas.

**Figure 17: Prioritized Buffer Prep Improvement List to AFR**

	<u>Idea</u>	<u>Projected Improvement</u>	<u>Feasibility</u>	<u>Recommendation</u>
Do First	Implement Standard Work	Decrease in C/T & variation <b>68.2 hrs/pur run (40%)</b>	Highly Feasible	Use the buffer prep process as a showcase for standard work in AFR
	Optimize buffer transfer rate a) Increase pressure b) Ensure optimized priming	Decrease in buffer transfer time: currently for 51 kL @ 35 L/min = 24 hr; projected @ 64 L/min = 13 hr <b>11 hrs/pur run (46%)</b>	Feasible	Increase pressure in automation, sustain any improvements with standard work
	Optimize & Standardize current titration procedures	Counted in Standard Work	Highly feasible	Ensure procedures are standardized
Investigate	Install Online pH Analyzer vs. Offline pH instrument	Decrease pH meas'm't & titration times, currently 15-30 minute meas'm't process	Needs more work (gage R&R, std work)	Focus on standard work for this procedure first. Determine implementation cost.
Investigate in high volume situation	Increase WFI inlet flowrate for T-4020 (~30% slower)	10-20 minutes/cycle, depending of buffer volume & tk utilization	Unknown	Further investigation
	Rationalize QS step	Reduced time for liquid/liquid mixing	Re-validation or PQ mixing study	Further investigation
Not recmd'd	Optimize mix times	None, PQ's exist for validated mix times	N/A	No action recommended

### *Presentation of Results & Recommendations to Key Stakeholders*

A formal presentation of the data summaries and findings was arranged for the Purification area and manufacturing management, with the goal of agreeing on a clear plan forward and committing to implementing the changes. The most impactful aspect of the presentation was showing the historical cycle time data and the potential of reducing variation and average cycle time. There was general approval and agreement to the efforts proposed by management.

### **3.5 Implement and Closeout**

The most important part of the APEX methodology is arguably implementation of and reflection on the improvements made by the team. Unfortunately, progress with implementation of the proposed prioritized process improvements was lower than expected due to other projects at AFR that required significant resources. Certain projects that are related to Lean and Operational Excellence were ongoing at the end of the internship. For example, 5S has been a steady effort that spread throughout the AFR facility, and a broader effort to consolidate "tribal

knowledge” that the operators had accumulated starting up and running the plant and process was pursued as a basis for future standard work. The process engineering group was also working on improving buffer prep by investigating a process technology to dilute more concentrated buffers to the needed specifications immediately before use in purification, thereby reducing the total volume of buffer needed to be prepared and stored.

The Operations Improvement team also implemented a broad training program to disseminate the basics of Operational Excellence to the plant, and focused training to prepare engineers, operators, associates, scientists, technicians, and managers to become project leaders. To date, over 200 employees at AFR received some level of training in Operational Excellence.

Tracking and trending production data was one weakness that was identified during the course of this project. Training on the use of OSI PI was being conducted for operators so that they can leverage the database and PI system for producing metrics and monitoring processes. Some analytical training was given to operators so that the analyses shown in this project could be reproduced for other efforts.

#### *Discussion of Guidelines for Standard Work in a GMP Environment*

Change control and the level of resources needed to effectively propose, approve, and implement a procedural or equipment change was noted to be a key roadblock for change and process improvement. This tension between conservativeness in ensuring quality versus openness to changes and improvements is a key challenge for those in the biotechnology and pharmaceutical industries.

This particular challenge can be addressed by establishing a global standard for Amgen’s manufacturing network. Frequently, there are site-to-site incongruencies in policies and procedures concerning change control. The first step is to standardize and potentially re-engineer the process to serve both goals of maintaining quality and compliance, and enabling process improvements to be implemented.

## **Chapter 4: Conclusions and Recommendations**

### ***4.1 Amgen Fremont***

The fact that there were no Industrial Engineering (IE) capabilities at the site led to the Operations Improvement group's involvement at site. Near the end of the internship, a full time manager responsible for operational excellence was recruited. However, for much of the time of the project, the difficulty of remote project management was one of the factors hindering full engagement and implementation of this specific buffer prep process improvement.

Many lessons were learned by the author and the team about remote project management:

- First, it is critical to engage the site's teams in the development of the process improvement ideas to increase their sense of ownership.
- Second, this project provided a good example of the ease and effectiveness of utilizing current information technology to download and analyze plant data remotely.

The site was running simultaneously under capacity while undergoing facility expansion. This capital project consumed a significant amount of resources, which is another factor hindering the implementation of buffer prep improvements. These facility improvements and expansion suggest that there may be an anticipated increase in either the volume of the current product or introduction of additional products to be produced in AFR in the future. Therefore, it is very important for the team to effectively analyze the facility's capacity and manage its bottlenecks through similar efforts as shown in this thesis. Given the organizational momentum at the company and site levels for operational excellence, there is no doubt that AFR will be able to improve its operations and build a strong culture of continuous improvement.

Recommendations were already given for specific actions on the buffer prep process above. However, some general observations and advice from this experience are offered:

- Focus on standard work and stabilizing performance of processes and operations. Without first understanding the performance, it will be near impossible to identify feasible goals for improvement.

- Continue with projects that engage the operations staff such as generating process readiness kits for complex procedures and implementing 5S. These will serve as a basis and foundation of achievement for more ambitious projects.
- Continue to encourage involvement from non-manufacturing groups such as the quality control lab and process development groups. Engaging the entire plant is critical so that Lean will not be seen as a manufacturing-only endeavor.
- For projects that have been approved, improvements estimated, and resources allocated, ensure consistent application of the APEX framework when reporting results to reinforce the training that has been given.

## ***4.2 Amgen Operational Excellence***

There was a need for greater alignment and effective use of resources for APEX efforts across the entire manufacturing network. Biweekly meetings held by the core team at Thousand Oaks with the network of IE and Lean practitioners joining via teleconference help serve this purpose through knowledge sharing, forming teams and working groups, and balancing resources for special projects and problems. However, attendance to this virtual meeting (teleconference) declined over time and a revitalization of this forum occurred during my internship to refocus the team and ensure engagement from the network. One lesson learned is that it is vitally important to maintain the forum of communication using Thousand Oaks as a hub so that best practices and resources can be effectively deployed. Practitioners at the site level often become highly engaged in the continuous improvement work they are intimately involved in and can lose sight of the company-wide engagement that is needed from them to ensure success in total operational excellence.

The Operations Improvement team made substantial progress in developing a coherent training program to start spreading the methods and tools of Operational Excellence and APEX. This aspect of Operational Excellence was kept centralized to maintain a consistent message.

It was observed that improvement projects were generated and managed in a decentralized fashion, which makes sense because:

- Lean espouses enabling the workforce, especially operators, to generate, implement, and maintain improvement ideas.
- The local teams of experts know the site-specific cultures and organizations very well so change is more likely to occur.
- Despite local project leaders and teams being responsible for execution and capture of benefits, there was centralized oversight and tracking of all of these projects for reporting purposes. This duality of oversight ensured consistent motivation to enact change.

There are many challenges facing such a large sustained effort to instill Operational Excellence for a large biotechnology company. Amgen's challenges are undoubtedly shared by other companies. Some of these challenges and recommendations to counteract them are:

- Prioritization of efforts: developing and applying a consistent methodology. There are usually many good ideas, but too many to pursue at the same time. Therefore, it is important to effectively prioritize and deploy resources. Amgen had made some progress developing a project idea validation process to prioritize projects.
- Generating a centralized approach to supplement the decentralized improvement projects. Value stream mapping of important products and their flow through the supply chain will help identify projects that may not be in the radar of site managers and project leaders.
- Breaking stereotypes and changing culture: the biotechnology culture is one of scientific innovation. Being science-based is one of Amgen's core values and framing Operational Excellence as part of that value is important for widespread support and adoption. However, the R&D culture of biotechnology may construe science as principally making discoveries in the laboratory rather than finding efficiencies in manufacturing. This view of the biotechnology culture needs to be broken for Amgen and other similar companies to be effective at operations.
- Bridging the gap of biotechnology and Lean with the right talent: Amgen was quite fortunate to have a strong core of individuals who have experience implementing similar projects in other industries as well as individuals who developed process improvement experience while working in biotechnology operations. Having both the insider and outsider points of view, while increasing the abilities of the workforce, will be vital to Amgen's success in Operational Excellence.

- Cross-organization/industry sharing. The biotechnology industry is primarily built on intellectual property and competitive advantage granted by regulators for being the innovator in a market. Thus, secrecy and rigorous control of information is part of the culture. However, other industries have made great strides by sharing of information between organizations. For example, the semiconductor industry, with the help of the US government, founded a consortium of integrated-circuit manufacturers to cooperatively research and develop semiconductor manufacturing technologies (May & Spanos, 2006). A similar model focusing on common manufacturing aspects such as utilities systems and buffer or media prep systems may be helpful. The Leaders for Manufacturing Program helps in this respect with cross-industry as well as cross-organization learning.
- Unify and align incentive structures to encourage operational excellence. Just as important as developing the proper metrics in a balanced scorecard, Amgen should ensure that the performance evaluation and rewards and recognition systems are also aligned with this major effort. This piece of change management is critical for success in changing and shaping behaviors in an organization. Amgen Operational Excellence is well-structured to ensure a holistic view and implementation plan to incorporate metrics, incentive, skills, and projects.

### **4.3 Conclusion**

The experiences from the effort at AFR and at Amgen Thousand Oaks in the Operations Improvement group have been very promising in terms of the chance that operational excellence will be successful. The company has already captured substantial cost reductions and savings from the efforts of this department. As long as the change agents maintain the outsider-insider perspective, then sustained change and process improvement should occur (Klein, 2004).

Despite the slow progress in this specific project at AFR, Amgen has been making steady progress and capturing significant cost savings throughout its network of manufacturing sites. They have followed an orderly process of characterizing the opportunities of various improvement ideas, devoted resources to pursuing projects, and have applied project management focus to capture and track financial benefits. Non-financial benefits are already

being captured. At AFR alone, the excitement and motivation to improve their operation was palpable. As long as commitment to the effort is maintained, this morale and support among the workforce will be maintained. Over 200 associates from AFR were trained in some level of Operational Excellence understanding. One critical enabler will be establishing a full time local project leader to manage future process improvement projects and this was already under way.

Using AFR as a model of a site that is behind others in the network that have full-time teams of local Lean project leaders, the future for Amgen's operational excellence efforts is bright. The cultural and organizational fit, leadership backing, and enthusiastic engagement by the workforce will enable Amgen to capture many future benefits from this effort.

#### ***4.4 Recommendations for Future Work***

Potential projects for an LFM intern include:

- Potential opportunity to optimize material flow and manufacturing using SAP as a scheduling and production control tool.
- Apply simulation software such as SuperPro by Intelligen to perform what-if scenario analysis on current plant and process configurations. Focus on one product's manufacturing process, find inventory optimization opportunities, and optimize speed and throughput.
- Streamline business processes to speed product development, batch QC and release, change control, and deviation management.
- End-to-end product optimization – focus on one product, construct value stream maps, and identify process improvement projects for a product's supply chain.

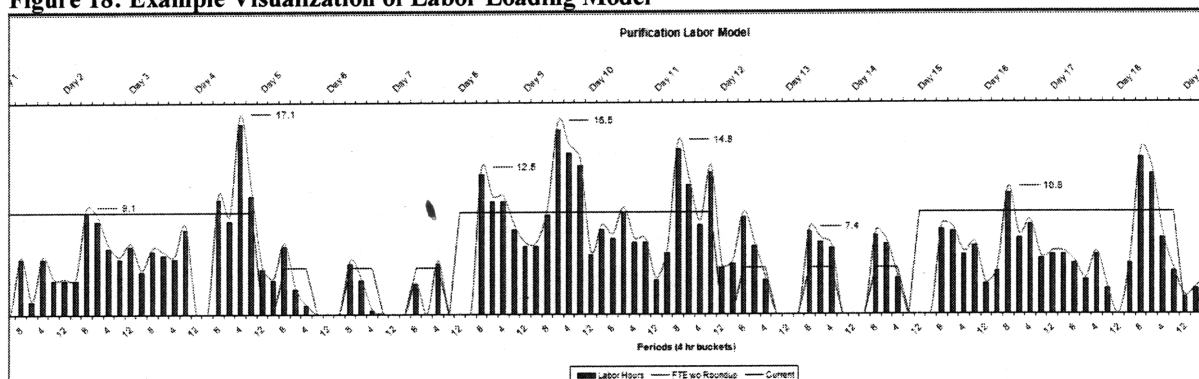


## APPENDIX: Labor Modeling and Balancing at Amgen Operations

### A.1 Concepts of Modeling Labor for Batch Processes

During this internship, labor load modeling and balancing was investigated as a process to characterize and predict the labor requirements given varying levels of customer demand. The Operations Improvement team generated a chart describing the amount of operator time needed for one production run/batch from AFR's production schedule and is shown below. The data from the project schedule was used to break down one day's activities into four-hour increments, so that theoretically, a plant would staff an area up to manage the peak labor demands. This would also be useful in scheduling to move, when able, activities to alleviate peak demands.

**Figure 18: Example Visualization of Labor Loading Model**



There were two goals of using this type of data from a plant: extend the direct labor model to determine theoretical staffing of indirect labor and overhead such as QC analysts, management, and warehouse materials associates using activity-based predictions; apply this tool across the manufacturing plant network to identify best practices and benchmarking.

An effort to find other similar models across Amgen was conducted. A database tracking QC laboratory analyst hours for different routine methods, along with demand patterns allowed the quality unit to effectively generate the same type of data for the lab. Product development also had a management system to guide the staffing of new product development projects as well. Externally, modeling and simulation tools for batch manufacturing such as Superpro have the

ability to aggregate labor resource data to generate labor demand charts as well as equipment loading charts (Petrides, Koulouris, & Siletti, 2002).

## ***A.2 Opportunities for Standardization***

No one standard existed for understanding the mechanics of labor demand on a process and staffing was achieved using previous data and experiences. This provided a great opportunity to analyze the labor demand (both direct, indirect/overhead) via an activity-based model across the manufacturing network. This effort would require extensive data collection, interviews with management, and potentially productivity analysis along with stochastic demand (from the customer) modeling.

A simple model of indirect staffing (quality assurance associates, supervisors, engineers, and management) was built during the internship to demonstrate the feasibility of such an effort using existing organizational data and direct labor/schedule data from AFR. This project idea along with a detailed description of the methodologies involved was proposed and transferred to the Operations Improvement team for future evaluation as a project.

## ***A.3 Conclusion***

The investigation into this predictive labor modeling and labor loading/balancing tool proved to be an effective way for management to visualize how they can adjust schedules and efficiently staff a process. Extending this idea across the organization using an activity-based model (similar in concept to activity-based cost accounting) will also help evaluate needs and improvement opportunities for indirect and overhead labor.

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